Assessment of Cardiac manifestations in patients with Scrub typhus in a tertiary care centre in South India

A Prospective Cohort Study

A dissertation submitted in partial fulfillment of the rules and regulations for MD General Medicine examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai, to be held in April 2015

DECLARATION

This is to declare that this dissertation titled "Assessment of cardiac manifestations in patients with Scrub typhus infection in a tertiary care centre in South India – A prospective cohort study"

is my original work done in partial fulfillment of rules and regulations for MD General Medicine examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2015.

CANDIDATE

Karthik. G

Post graduate Registrar

General Medicine

Christian Medical College

Vellore

CERTIFICATE

This is to certify that the dissertation entitled, "*Assessment of cardiac manifestations in patients with Scrub typhus infection in a tertiary care centre in South India – A Prospective cohort study*" is a bonafide work done by

Dr. Karthik. G

towards the partial fulfillment of rules and regulations for MD General Medicine degree examination of the Tamil Nadu Dr. M.G.R Medical University, to be conducted in April 2015.

GUIDE

Dr. John Victor Peter

Professor

Dept of Medicine

Christian Medical College

Vellore

CO – GUIDES

Dr. Thambu David Sudarsanam (Professor and Head, Medicine Unit II)

Dr. Kishore Pitchamuthu (Professor, Medicine Unit IV)

CERTIFICATE

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Dr. Karthik. G

towards the partial fulfillment of rules and regulations for MD General Medicine degree examination of the Tamil Nadu Dr. M.G.R Medical University, to be conducted in April 2015.

PRINCIPAL

Dr. Alfred Job Daniel
Professor
Dept of Orthopedics
Christian Medical College
Vellore

HEAD OF THE DEPARTEMENT

Dr. Anand Zachariah
Professor and Head
Department of Medicine
Christian Medical College
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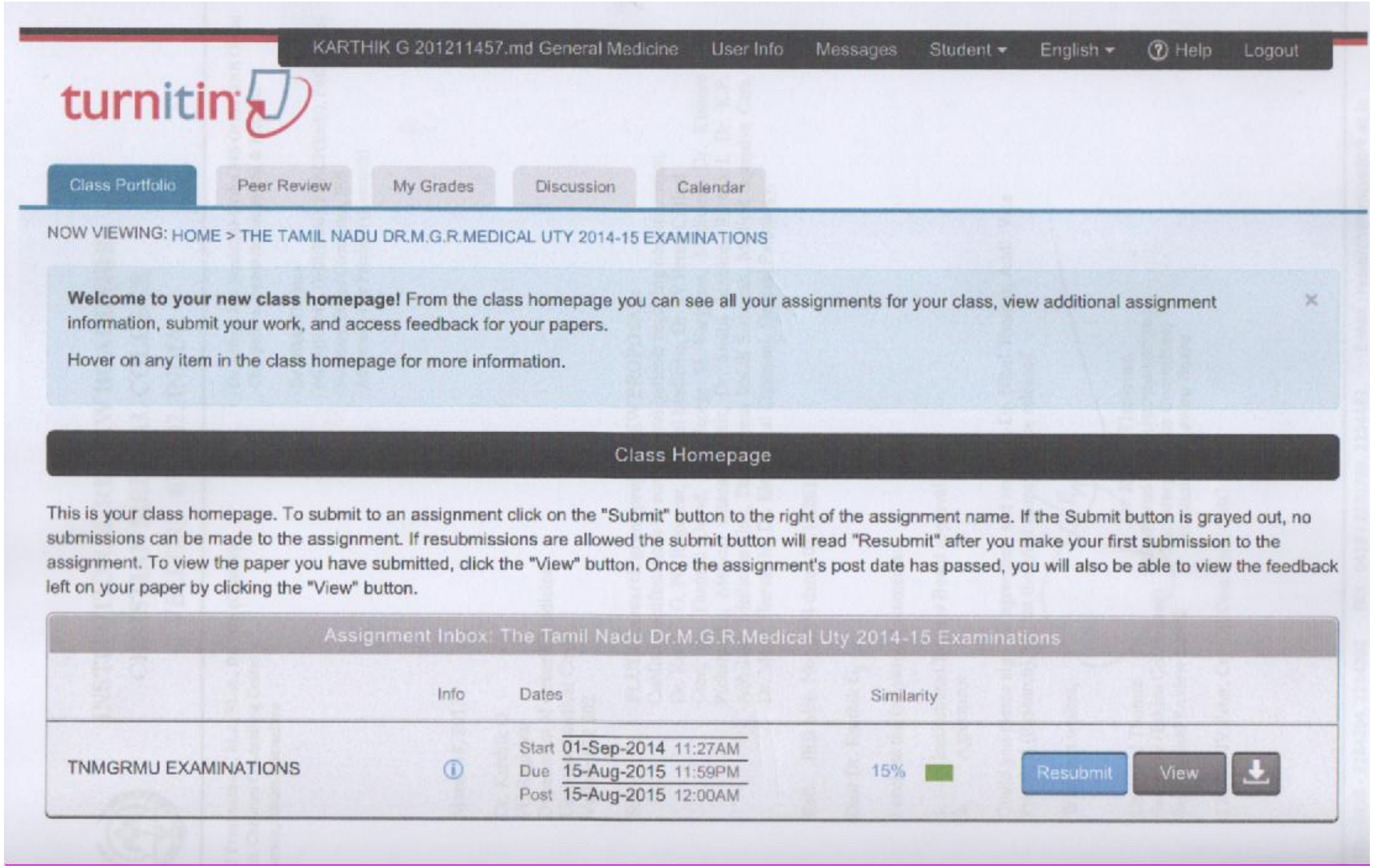
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March 14, 2013

Dr. Karthik G
PG Registrar
Department of General Medicine
Christian Medical College
Vellore 632 002

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Dear Dr. Karthik G,

I enclose the following documents:-

1. Institutional Review Board approval
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Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

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Dear Dr. Karthik G,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Cardiac manifestations in scrub typhus patients requiring hospitalization." on December 5, 2012.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Patient Information Sheet (English, Tamil and Telugu)
3. Consent Form (English)
4. Proforma
5. Cvs of Drs. Karthik G, Thambu Daivd, , JV Peter, George M Varghese, Kishore Pichamuthu, Sudha Jasmine, Ramya I, K.P. Abhilash, Thomas Isaiah Sudarsan, Marie Therese M, . Elanthenral Sigamani,
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Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Internal, Clinician
Dr. Priya Abraham	MBBS, MD, PhD	Professor, Virology, CMC	Internal, Clinician
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Dr. Denny Fleming	BSc (Hons), PhD	Honorary Professor, Clinical Pharmacology, CMC.	Internal, Pharmacologist
Dr. Simon Rajaratnam	MBBS, MD, DNB (Endo), MNAMS (Endo), PhD (Endo), FRACP	Professor, Endocrinology, CMC	Internal, Clinician
Dr. Anup Ramachandran	PhD	The Wellcome Trust Research Laboratory Gastrointestinal Sciences	Internal
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The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent. And on completion of the study you are expected to submit a copy of the final report.

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A sum of Rs 40,000/- (Rupees Forty thousand only) will be granted for 12 months. A subsequent installments of 40,000/- each will be released at the end of the first year following the receipt of the progress report (Total amount 80,000/- for 2 years).

Yours sincerely

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MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
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,
CC: Dr. JV Peter, Critical Care Unit, CMC

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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TITLE: Assessment of cardiac manifestations in patients with scrub typhus infection in a tertiary care centre in south India.

DEPARTMENT: Department of General Medicine

NAME OF THE CANDIDATE: Karthik G

DEGREE AND SUBJECT: MD General Medicine

NAME OF THE GUIDE: Dr John Victor Peter

KEY WORDS: myocarditis, scrub typhus

WORD COUNT: 407

OBJECTIVES:

This study was done to known the spectrum of cardiac manifestations in patients with scrub typhus infection and to determine the incidence of myocarditis in these patients. This study identifies the factors contributing to myocarditis, and to compare the outcomes in patients with and without myocarditis and to know the mechanism of myocarditis.

METHODS:

This prospective cohort study was conducted in a teaching institute in south India; all patients with acute febrile illness and a clinical syndrome suggestive of scrub typhus infection and fulfilling the diagnostic criteria were recruited and followed up till their hospital stay. A diagnosis of myocarditis was considered in patients with myocardial injury (troponin level measured more than 14 pg/ml) with coexisting myocardial dysfunction (left ventricular ejection fraction less than 50%). Descriptive statistics were obtained for all variables in the study.

Categorical and continuous variables were compared for outcome by using the fisher's exact test and student t test respectively. All continuous data were expressed as mean ± SD unless the data was not normally distributed. A p value of < 0.05 was considered statistically significant for all analysis. The presence of myocarditis, myocardial injury and dysfunction were correlated with mortality. This was expressed as odds ratio (OR) with 95% confidence interval (CI). A multivariate logistic regression analysis was performed to assess and identify those factors which were independently associated with myocarditis.

RESULTS AND CONCLUSIONS:

This prospective cohort study was conducted over a period of 20 months (June 2012 to January 2014). The study cohort comprised of 81 patients with a mean ± SD age of 49.41 ± 16.07 and presenting at 8.11 ± 3.11 days of illness. There was a slight female predominance observed, with female: male ratio of 1.3:1. In this cohort of scrub typhus patients the cardiac manifestations varied from asymptomatic patients with non specific ECG findings to myocarditis and cardiogenic shock. The incidence of myocarditis was 21%. Myocardial injury was seen in 61.7% and myocardial dysfunction was observed in 30.9% participants. A mild grade of diastolic dysfunction was observed in 18% of the study participants. Pericardial involvement was seen in 51% in the form of mild to moderate pericardial effusion. ECG changes were non specific; sinus tachycardia was the predominant ECG finding in this cohort. The development of myocarditis increased the need for ventilation, prolonged the duration of ICU and hospital stay. There was no biochemical, hematological or physiological factors predicting myocarditis and myocarditis was not associated with worse mortality in our cohort.

1. INTRODUCTION

Scrub typhus, a rickettsial infection caused by *Orientia Tsutsugamushi* is endemic to a part of the world known as the "tsutsugamushi triangle" which extends from Japan to Australia, and to Pakistan and Afghanistan. Since the 19th century, scrub typhus is reported more and more frequently. It accounts for nearly fifty percent of the cases of acute undifferentiated febrile illness in our hospital(1). It causes significant morbidity and mortality; in a cohort of 116 critically ill patients, the mortality rate was 24% (2). Clinical features may vary from acute febrile illness without localizing symptoms or signs to multi-organ involvement leading to death. It is known that scrub typhus can cause myocardial dysfunction but the magnitude of involvement and the impact of myocardial dysfunction and injury on various outcomes are unknown. In other disease processes such as severe H1N1 infection, myocarditis occurs frequently and is associated with increased mortality (3). As symptoms are non-specific, the diagnosis may be delayed or missed.

The contribution of myocardial disease to severity of illness and death in patients with scrub typhus is not established. As not all scrub typhus patients develop myocardial involvement, knowing what predispose them may help in early recognition. Scrub typhus causes vasculitis due to disseminated endothelial infection of the small vessels and by secondary immune mediated mononuclear inflammatory reaction. Myocarditis occurs due to disseminated endothelial infection of the small vessels or by secondary immune mediated mononuclear inflammation(4). The frequency and extent of cardiac involvement in scrub typhus is not known.

2. AIM

To characterize the cardiac manifestations in patients presenting with scrub typhus infection, hospitalized in tertiary care centre in South India.

3. OBJECTIVES

1. To study the spectrum of cardiac manifestations in scrub typhus infection.

2. To evaluate the incidence of myocarditis

3. To compare the outcome of scrub typhus patients with and without myocarditis.

4. To study the factors contributing to the development of myocarditis in Scrub Typhus.

5. To study the mechanism of myocarditis.

4. REVIEW OF LITERATURE

4.1 NATURAL HISTORY

Scrub typhus is a mite borne zoonotic rickettsial infection, the causative organism being *Orientia tsutsugamushi*. It is seen in the terrain areas of the 'tsutsugamushi' triangle which is a geographical region comprising South east Asia and Southwest Pacific (5). Scrub typhus was known as early as the 3rd century in China; however the magnitude of the disease was evident in the 2nd world war as many soldiers were victims of the chigger mite. Tsutsugamushi is a term with Japanese origin for tsutsuga which meant "illness" and mushi: insect or creature″.

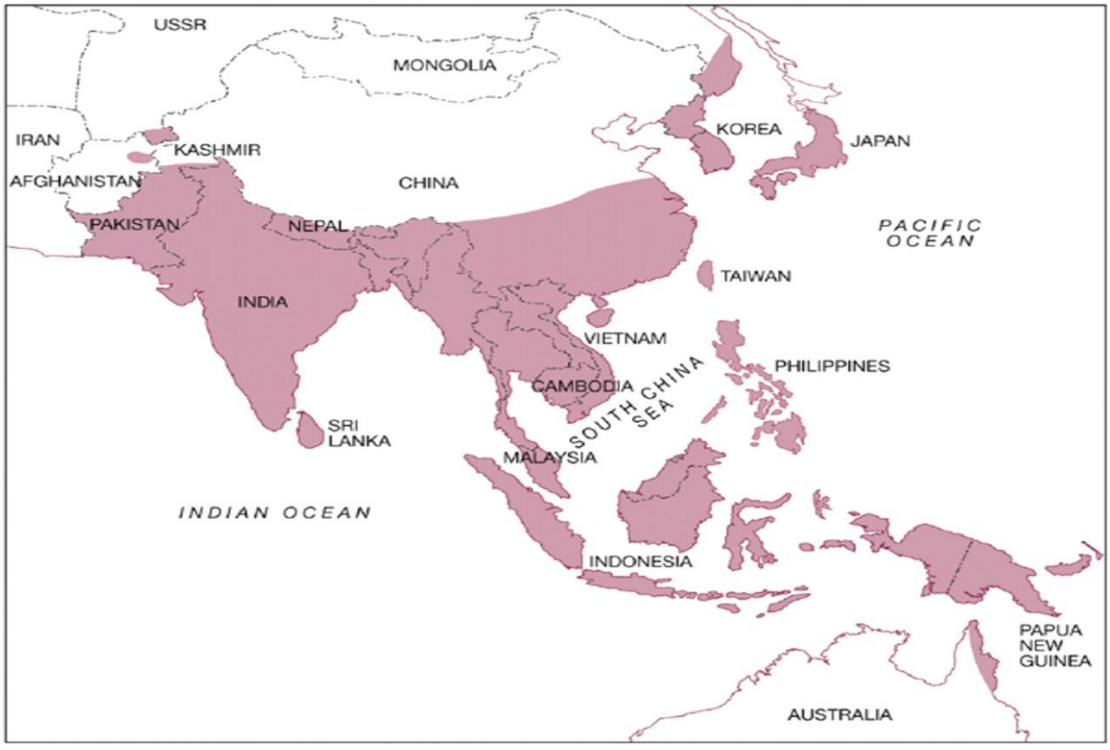


Figure 1 –'Tsutsugamushi' TRIANGLE

Scrub typhus is endemic to China, Japan, India, Pakistan, Korea, Thailand, Taiwan and Malaysia, and in the north tropical regions of Australia. Taiwan is the centre of the tsutsugamushi triangle; however the reported incidence is highest in Korea (6). The annul new case detection is about 1 million (7).

The first reported cases in India were in 1934, in Himachal Pradesh (8). Scrub typhus has been increasingly reported as a significant cause of febrile illness in many parts of India (5,9,10). A study done in CMC Vellore in 2007 showed 47.5% of the cases of acute undifferentiated febrile illness in south India were due to scrub typhus (1).

4.2 LIFE CYCLE

The disease is caused in humans following the introduction of *Orientia tsutsugamushi*. It is propagated by the bite of a larval-stage of trombiculid mite (chigger) (4, 5). Occupation associated with significant exposure to bushes and grasses, which are the breeding ground of the mites is found to be a common way by which the individuals acquire this disease (6). These mites have a four-stage life cycle namely egg, larva, nymph, and adult which is summarised in Figure 2 (6). The feeding behaviour of the larva is peculiar in that, it feeds only one time. After the blood meal, it detaches itself from the host and subsequently matures. The mature form is the nymph which later becomes an adult. They are free living parasites in the soil. Humans are accidental hosts with small rodents and mammals being the definitive hosts.

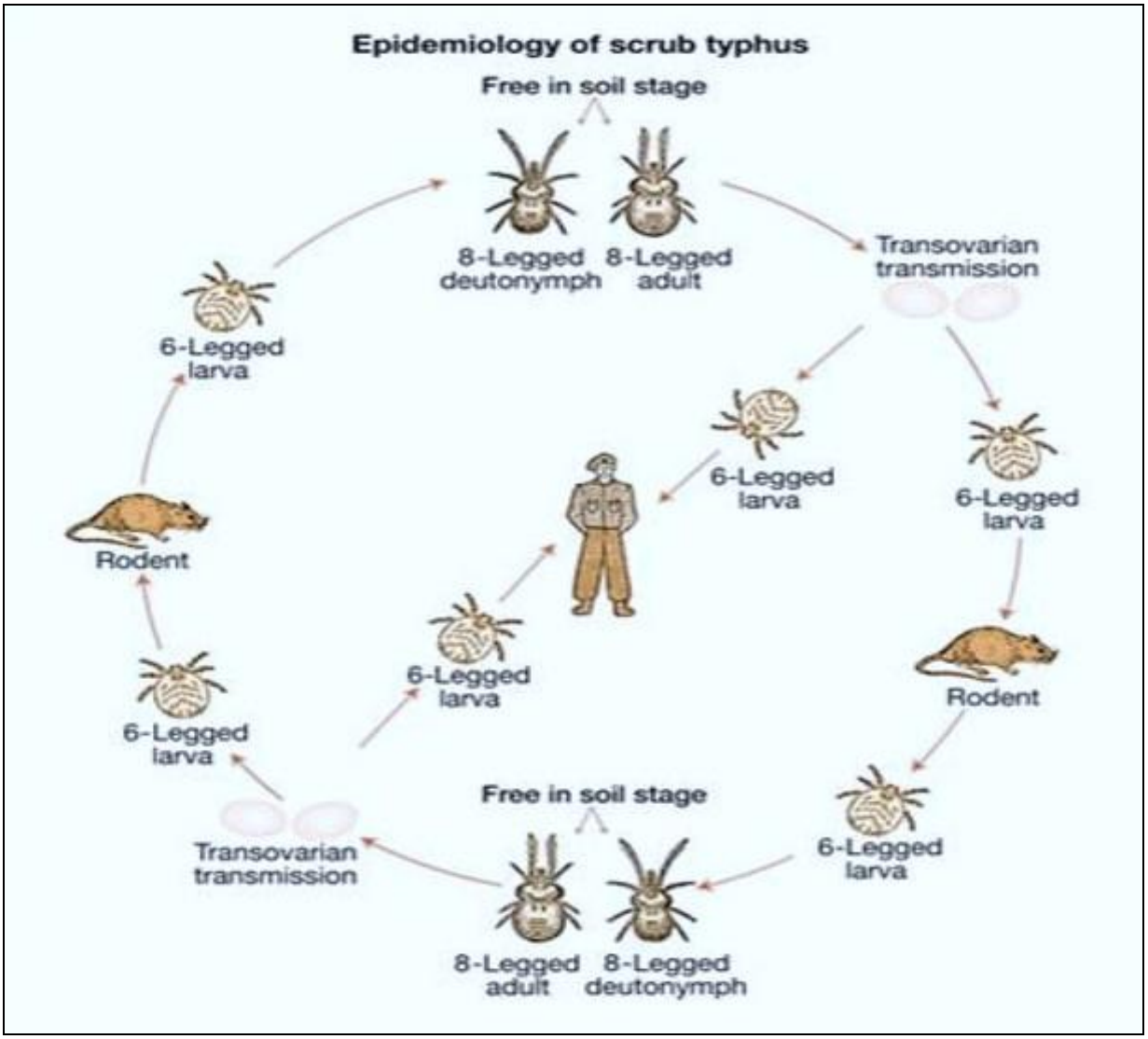


Figure 2 – LIFECYCLE OF SCRUB TYPHUS

There have been no reports of contact transmission of infection between individuals (6). The impact of temperature and humidity on the parasite influences the epidemics (6). Transmission occurs year-round in tropical areas and in the subcontinent during the rainy season(7).

4.3 MICROBIOLOGY

O. tsutsugamushi is a gram-negative coccobacillus. It is different from the typhus group *rickettsiae* both in terms of genetic composition as well as cell wall composition (O.*tsutsugamushi* does not have a slime layer on its outer membrane). It requires a cell enriched media for propagation.

O. *tsutsugamushi* is unique in its method of dissemination. Following infection of the host cells, it incorporates the host cell membranes and emerges as budding forms from the infected cells. It then undergoes phagocytosis by the neighboring host cells. Phospholipase A2 (rickettsial) mediates the entry into host cells, which further leads to release of phagosomes causing injury to host (11). They undergo rapid and widespread dissemination following the initial inoculation into the skin. The presence of O. *tsutsugamushi* was identified on staining mononuclear cells in the peripheral blood in three out of seven patients studied with acute scrub typhus (12).

Three major variants or strains of O. tsutsugamushi have been identified. They are Karp, Kato and Gilliam. Infection with one strain does not prevent reinfection with a different strain.

4.4 PATHOGENESIS

The pathogen multiples at the site of inoculation following the bite, and subsequently induces local and systemic manifestations of infection. The severity of illness depends on both host and pathogen related factors. Pathogen related factors may be attributed to the fact that different strains (Karp, Gilliam and Kato) of O. Tsutsugamushi may contribute differently to disease severity.

The bacterium multiplies and disseminates within the human host and its principal target being the endothelial cells. They have been located in endothelial cells of heart, lung, brain, liver, kidney, pancreas, skin and also isolated from macrophages of liver and spleen in post mortem samples (13). Initially it was thought that the organism gains entry to the target organs through the lymphatic system. However in 2001, Walsh et al (12) demonstrated the pathogen within mononuclear white blood cells in patients with acute infection, suggesting the possibility of a direct blood borne spread.

The immune response induced by O. *tsutsugamushi* is a combination of humoral and cell mediated immunity. The rise of cytokines during an acute infection was demonstrated as far back as 1997 by Iwasaki et al (14). In a small series of patients, they have shown a significant rise in macrophage colony stimulating factor (M-CSF), interferon gamma (IFN-γ) and granulocyte colony stimulating factor (G-CSF).

Only a few patients showed a rise in tumour necrosis factor (TNF-α) during the infection but it continued to rise during convalescence in those who had severe disease. These observations demonstrated that the macrophage and T lymphocyte response may be the driving factor in immunity against infection.

More recently, Fost et al (15) have demonstrated indirect evidence for cytotoxic lymphocyte (cytotoxic T cell and natural killer cell) activation during acute infection that may play a key role in destroying the infected host cells. The parasite has evolved to evade the immune mechanisms of the host. In view of the high mortality rate of untreated disease, these mechanisms are of clinicopathological significance.

Cho et al (16) showed that live O. *tsutsugamushi* down regulates the expression of the glycoprotein 96 (gp96) in infected macrophages and endothelial cells compared to non- infected cells in cell culture. This molecule is expressed in the endoplasmic reticulum of cells and plays a central role in major histocompatibility complex class I (MHC I) mediated antigen presentation, functioning of dendritic cells, antibody production and cross priming of immune cells (16). Suppression of this glycoprotein may be one mechanism by which the pathogen neutralizes the host immune response.

4.5 RISK FACTORS

Scrub typhus is characteristically a geographically focal disease, transmission is seen in the south East Asian and Pacific regions that consist of focal locations of scrub vegetations. The mites live on these vegetations and the moisture and temperature conditions are ideal for propagation of chiggers and their small rodent hosts. When humans enter these mite islands the risk of disease transmission from chigger bites may be extremely high. Farmers account for approximately fifty percent of all reported cases (6). Scrub typhus infection is strongly associated with people working in fields (17). Scrub typhus is seen more commonly in people aged 40 to 60 years of age, but young children have higher rates of infection than young adults (18). Even though scrub typhus infection is seen throughout the year the incidence is highest during June to October (19).

4.6 CLINICAL MANIFESTATIONS

Scrub typhus causes a spectrum of illness from asymptomatic mild and self-limiting to fatal illness with multiorgan dysfunction. The incubation period following successful inoculation ranges from an average of 6 to 21 days. Initial symptoms of the disease include fever, myalgia, headache, cough and gastrointestinal symptoms (20). The severity of the symptoms depends on the host susceptibility and the virulence of the bacteria or both (20). The classic case description includes an eschar at the site of chigger feeding, regional lymphadenopathy and a maculopapular rash (1,20).

Cutaneous manifestations appear five to eight days after the onset of fever. A macular or maculopapular rash occurs on the trunk which could progress centripetally to involve the limb. Presence of an eschar at the wound site is the diagnostic clue of significance (7). An eschar is seen at sites where the skin surfaces are in contact or the clothes bind, such as the neck, axilla, waist, groin and inguinal area. It is seen less frequently on South Asians in view of the dark skin and is easily found on Caucasian and East Asian patients. It starts as a papule, progresses to develop central necrosis followed by development of a blackened crust surrounded by an erythematous halo simulating a cigarette burn (7). Eschar can be detected in 46-86% of scrub typhus patients (21). Kundavaram et al (22) found significant differences in the distribution of eschar among males and females. In females eschar was predominantly seen in the chest and abdomen (42.3%) whereas in males it was seen mostly in the axilla, groin and genitalia (55.8%). The most likely places to find an eschar were the groin and abdomen. Most common systemic findings include generalized lymphadenopathy and splenomegaly (1,20).

In patients with a history of exposure in a geographic area, endemic to scrub typhus presenting with fever, rash, eschar, generalized or regional lymphadenopathy, scrub typhus

should be considered in the differential diagnosis. Other differentials to be considered include rickettsial pox, dengue, Mediterranean spotted fever, leptospirosis and murine typhus.

4.7 COMPLICATIONS

Systemic complications of scrub typhus which are commonly reported include interstitial pneumonia, meningoencephalitis, acute renal failure and gastrointestinal bleeding. Multiple organ dysfunction is also a common entity. Varghese et al (23) have reported similar complications in a cohort of 623 patients from south India; multi-organ dysfunction was seen in one third of the patients and the case fatality rate was 9%.

Patients with shock requiring vasoactive agents, central nervous system dysfunction and renal failure were independent predictors of mortality. The incidence of various organ dysfunctions in a cohort of 116 critically ill patients with scrub typhus revealed that respiratory organ dysfunction predominated and was present in 96.6% (2). Cardiovascular dysfunction was present in 61.7% and renal and hepatic dysfunction in 63.8% or patients. Ninety one (85.2%) patients had dysfunction of three or more organ systems and mechanical ventilation was required in 102 (87.9%) patients. The mortality in this cohort of patients was 24%, duration of fever and APACHE II score independently predicted mortality (2). In a case control study comparing severe scrub typhus with those with mild disease, Kim et al (10) observed that age, absence of eschar, leucopenia and hypoalbuminemia to be associated with severe complications. It is evident that patients with scrub typhus infection typically present with significant physiological derangement of multiple organ systems. Despite the high prevalence of multi-organ dysfunction and the severity of illness, scrub typhus patients had fewer than predicted mortality.

4.8 DIAGNOSIS

As with all rickettsial diseases, no laboratory test is diagnostically reliable in the early phases of scrub typhus. The disease is usually recognized when clinicians correlate the presence of compatible clinical signs, symptoms and laboratory features, with epidemiologic clues (e.g., recent exposure to environments in which chiggers are known or suspected to be present). Most patients with severe illness develop thrombocytopenia, transaminitis, hyperbilirubinemia, and deranged creatinine. Leucopenia as well as leukocytosis can occur, but most have a normal white blood cell count.

Serologic assays (IFA, indirect immunoperoxidase and enzyme immunoassays) are the mainstays of laboratory diagnosis, and PCR amplification of *Orientia* genes from eschar and blood is also effective.

4.9 TREATMENT

Chloramphenicol was the first drug reported to be effective in management of scrub typhus, and is the first line agent in many endemic areas. Intravenous doses or oral doses of 250 to 500 mg every sixth hourly is effective. Doxycycline (100 mg orally or intravenously twice daily) is now the standard of care. Azithromycin can be used as an alternative agent in special circumstances. Doxycycline resistant scrub typhus is emerging especially in parts of Thailand, hence need for azithromycin or high antibiotic regimen is warranted.

4.10 CARDIOVASCULAR COMPLICATIONS IN SCRUB TYPHUS

The incidence of myocarditis associated with scrub typhus is unknown. Myocardial involvement in scrub typhus was first described by Levine's post-mortem findings in a series of 31 scrub typhus patients during World War II. He described varying degrees of myocardial inflammation in 25 (81%) cases (24). However the contribution of myocardial disease to the cause of death in these individuals was not established as scrub typhus causes multiorgan dysfunction. *Orientia tsutsugamushi* an intracellular parasite causes destruction of endothelial cells and perivascular infiltration of leukocytes resulting in focal and disseminated vasculitis and perivasculitis involving the small blood vessels (25). Myocarditis may occur during acute rickettsial infection due to disseminated endothelial infection of the small vessels or by secondary immune mediated mononuclear inflammatory reaction. This could account for the myocardial inflammation with resultant left ventricular dysfunction causing significant mortality due to cardiac involvement in the disease (25).

In scrub typhus myocarditis, nonspecific damage to myocytes, with minimal necrosis, can occur as a result of vascular endothelial damage and an inflammatory response consisting of infiltrating lymphocytes, monocytes, plasma cells associated with haemorrhage and oedema induced by adjacent infection. Lack of coronary artery involvement has been demonstrated by histopathology and coronary angiography (24,25). Similarly, native heart valves are spared. Focal petechial haemorrhages observed in many organs have been noted in the subendocardium and subepicardium (24,26). The lack of significant myofibril necrosis may explain the absence of chronic cardiac sequelae (26). Proliferation of *Rickettsia tsutsugamushi* was observed in the vascular endothelial cells of the myocardium, indicates that endomyocardial biopsy may be a useful diagnostic test to prove myocardial involvement in *R. tsutsugamushi* (25).

4.10.1 CLINICAL FEATURES IN MYOCARDITIS

The clinical findings of myocarditis are nonspecific and indistinguishable from other aetiologies and may include fever, shortness of breath, and orthopnea (25,26). Clinical manifestations form a large spectrum which might occur as ECG abnormalities which are not symptomatic to fatal cardiogenic shock. Individuals with fulminant myocarditis present with severe hemodynamic compromise requiring vasopressors and / or mechanical circulatory support (27).

Physical examination may reveal elevated jugular venous pulsations, rales, a ventricular gallop, or systolic murmur in the apex (25,26).

4.10.2 ELECTROCARDIOGRAPHIC FINDINGS IN SCRUB MYOCARDITIS

Electrocardiogram (ECG) abnormalities in scrub typhus have been studied. Cardiovascular complications of scrub typhus were more frequent in the pre antibiotic era. Fang et al (28) compared ECG findings in 98 cases of scrub typhus infection with 101 asymptomatic normal individuals. Occurrence of flat T waves in the precordial leads to tall and peaked T waves in leads V2-4 was noted in both acute and convalescent stages. Occurrences of sinus arrhythmia with some beats below 60 per minute in the convalescent stages were more frequent. ECG abnormalities were commonly seen with acute illness.

In the acute phase of the infection bradycardia predominates and in the convalescent stage, sinus arrhythmia, prominent u waves and T wave abnormality predominates (29). The use of appropriate antibiotics has reduced the complications of scrub typhus in the antibiotic era. In a recent study from Korea, Kim et al (30) showed the presence of an ECG abnormality in more

than 30% of scrub typhus patients. Scrub typhus patients with an arrhythmic ECG at presentation had associated elevated blood urea nitrogen (BUN) and creatinine levels. When these patients were followed up, the patients with persistent abnormal ECG were associated with high BUN, creatinine levels, and had an increased rate of ICU admission with prolonged stay. The presence of ECG abnormalities in scrub typhus patients are non specific and do not reflect cardiac involvement. It necessitates further evaluation in the form of cardiac enzymes and echocardiography study.

4.10.3 CARDIAC BIOMARKERS IN MYOCARDITIS

Serum cardiac biomarkers such as troponin (I and T) and creatinine kinase (CK) are routinely assessed in patients with clinical suspicion of myocarditis, but are limited by a low predictive value. In a study by Lauer et al (31), out of 80 patient with suspected myocarditis only 28 (35%) had elevated troponin. The sensitivity of Troponin T levels at a cutoff >0.1 ng/mL was found to be 53% and a specificity of 94% to predict lymphocytic myocarditis. A positive predictive value of 93%, and a negative predictive value of 56% was identified in lymphocytic myocarditis (31)(32). Smith and coworkers (32) in the Multicenter Myocarditis trial examined the value of troponin I in autoimmune myocarditis. The sensitivity of an elevated troponin I for the cohort was low (34%), however it was found to have a high specificity (89%). The sensitivity improved with a shorter duration of symptoms (<4 weeks) (32) and it also had an acceptable positive predictive value at 82%. Hence it is recommended to measure either troponin T or I whenever a diagnosis of myocarditis is suspected.

4.10.4 IMAGING IN MYOCARDITIS

Non invasive modalities of imaging techniques of diagnostic importance include echocardiography, imaging (gallium or indium- labeled antimyosin antibodies) and magnetic resonance imaging (MRI). They aid in the diagnosis of myocarditis.

The recommended standard of care for initial evaluation of patients with suspected myocarditis is Echocardiography. Pinamonti et al (33) in their retrospective study, analyzed the echocardiography findings among 42 patients, who had proven biopsy confirmed myocarditis due to various etiologies. Left ventricular dysfunction was a common finding (69%). Left ventricular enlargement was minimal or absent, hence suggesting other conditions causing acute dilated cardiomyopathy. Right ventricular dysfunction occurred in 23% of the cohort. Patients who presented with history of chest pain or features of heart block had preserved normal ventricular size and function. Regional wall motion abnormalities were seen in 64% of the cohort. Left ventricular hypertrophy was seen in 15% of patients and it showed complete resolution over several months. Thus, echocardiography findings can be varied but relatively nonspecific. However echocardiogram is the key noninvasive method of detecting impaired ventricular function in suspected myocarditis, even when subclinical (33,34).

4.10.5 ECHOCARDIOGRAPHY: TO ASSESS CARDIAC FUNCTION

The following parameters of cardiac functions are assessed by a non invasive imaging technique - Echocardiography.

Cardiac Output (CO) and Stroke Volume (SV)

Cardiac output is calculated by echocardiography through any structure, which will be sufficient enough to measure cross sectional area and also to gauge the velocity of blood flow. This could be through any of the valves, the pulmonary artery or the aorta.

The left ventricular outflow method is the easiest place to measure cardiac output and has the least variability.(35). The left ventricular outflow tract (LVOT) diameter changes very little through the systole and the diastole. It is assumed to be a constant variable and it closely approximates a circle. The LVOT diameter is measured during systole in the parasternal long axis view, next to the attachment point of the leaflets. The cross sectional area (CSA) is calculated by the machine.

The velocity of the blood flow against the time duration of systole is measured by the LVOT velocity time integral (VTI), in the units of cm. It is measured by angulating the transducer towards the chest wall, in the apical five chamber view. The PWD cursor is guided on the LVOT and is kept as close as possible to the aortic valve, excluding the sample volume. Application of digital software online helps to trace out the VTI by ultrasound machine.

The following are required for cardiac output calculation:

1) LVOT diameter

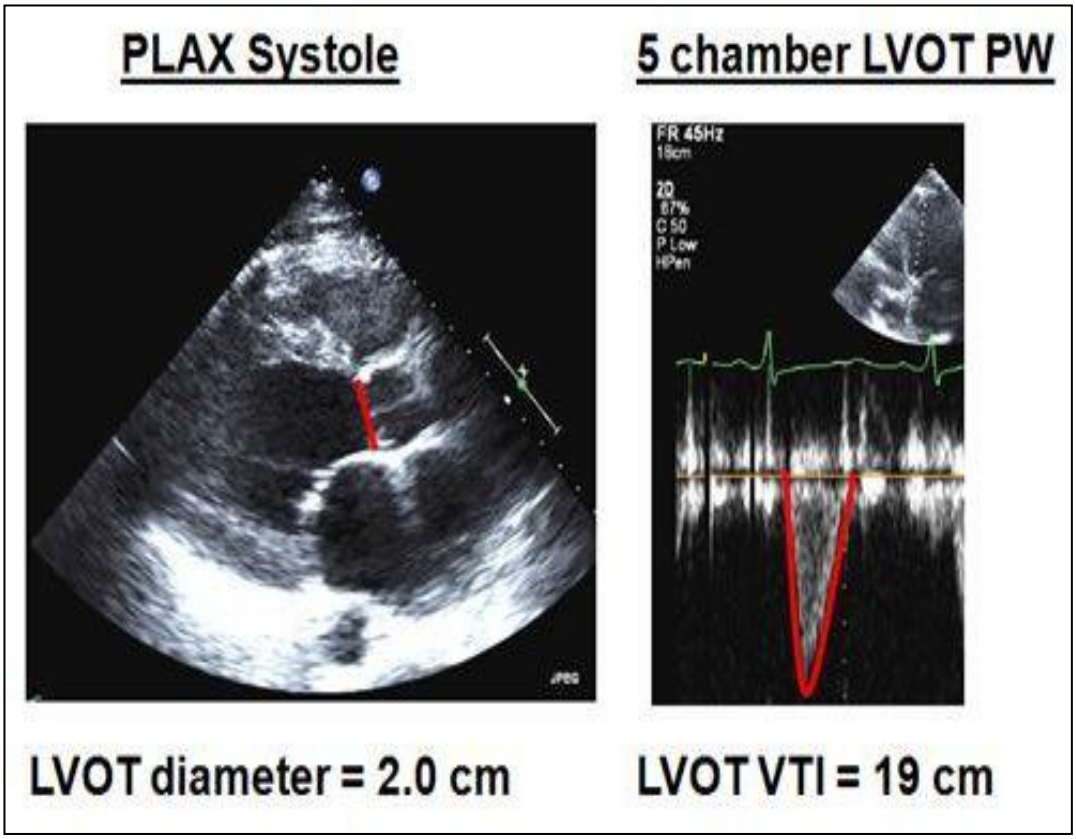
2) Heart rate

3) LVOT VTI

Cardiac output = Heart Rate x Stroke Volume

Stroke Volume= LVOT area x LVOT VTI

= π (LVOT diameter/2) ^2 x LVOT VTI.



Cardiac index (CI)

This parameter derives a relationship between the cardiac output (left ventricle per minute) to the body surface area. It hence correlates cardiac performance to the individual's body size. It is measured in terms of liters per minute per meter square. ($L/min/m^2$).

Cardiac index (CI) = cardiac output (CO) / basal surface area (BSA)

The cardiac index at rest is 2.6–4.2 $L/min/m^2$.

The cardiac index is often used in medical as well as cardiac intensive care medicine. It is a useful indicator of the cardiac functioning as a pump .It correlates directly, the total blood volume pumped by the heart with the body surface area of the individual.

Cardiogenic shock is a presence of hypotension with a combination of low cardiac index (less than 1.8 L/min/$m^{2)}$.

Stroke volume index

Stroke volume (**SV**) is the blood volume pumped from a ventricle with each heart beat. This is calculated by deducting the blood volume at the end of heart beat (end systolic volume) from the blood volume prior to the heart beat (end diastolic volume).This is done by measuring the volumes of ventricles from an echocardiogram. This term stroke volume can be applied to either of the two ventricles of the heart; however it commonly refers to the left ventricle. Each ventricular stroke volumes are generally equal and in a healthy 70 kg man measures approximately 70 mL.

The product of heart rate with blood volume is called stroke volume, which determines the cardiac output. Stroke volume can also be used to calculate ejection fraction, which is stroke volume divided by end-diastolic volume. Certain conditions and disease states decrease stroke volume. However; the parameter stroke volume correlates well with cardiac function.

Men have higher stroke volumes on an average than women. This is due to the larger size of the heart. Stroke volume is dependent on factors such as contractility, heart size, duration of contraction, after load and preload (end-diastolic volume).

The method of correlating stroke volume to body size of an individual is called Stroke volume index (SVI). This is calculated by the formula:

SVI = SV / BSA

SYSTEMIC VASCULAR RESISTANCE INDEX

The resistance offered to the free flow of blood, which must be overcome to successfully push the blood through the circulation is called as vascular resistance. The resistance of the peripheral circulation is called systemic vascular resistance (SVR) and is also called as total peripheral resistance. The resistance offered by the pulmonary vasculature is known as the pulmonary vascular resistance (PVR). A decrease in the diameter of the blood vessel is called vasoconstriction, which in turn increases SVR, whereas vasodilatation is an increase in diameter, which causes a decrease in SVR.

This is measured by using the Units such as $dyn \cdot s \cdot cm^{-5}$, Pascal seconds per cubic metre ($Pa \cdot s/m^3$) or it can also be derived by cardiac output (measured in l/min) and pressure (measured in mmHg) given as mmHg·min/l. This is used by pediatric cardiologists, and is referred to as hybrid reference units (HRU), also called as Wood units. By multiplying 8 Wood units can be converted to $MPa \cdot s/m^3$ or to $dyn \cdot s \cdot cm^{-5}$ by multiplying by 80.

SVR is defined by using the analogy of ohms law. This is measured by the ratio of drop in mean pressure to the cumulative flow in the systemic circulation. The basis of calculating resistance is that flow is equal to driving pressure and is divided by the resistance. The systemic vascular resistance can hence be calculated in units of $dyn \cdot s \cdot cm^{-5}$ as

$$\frac{80 \cdot (mean\ arterial\ pressure - mean\ right\ atrial\ pressure)}{cardiac\ output}$$

Systemic vascular resistance index (SVRI) is a method to correlate the systemic vascular resistance to the size of the individual. This following formula can be applied to calculate:

SVRI= SVR / BSA

A low SVRI is seen in vasoplegic shock. A high SVRI indicates a cardiogenic or hypovolemic shock. This is a useful tool in assessment of the type of shock.

Assessment of left ventricular diastolic function and filling pressures

Diastolic dysfunction of the left ventricle is common in critically ill patients. The presence of diastolic dysfunction in myocarditis has been described in lymphocytic myocarditis as described by James et al (36), an abnormal diastolic filling pattern was seen in 29 of the 30 patients (97%) studied. A restrictive pattern of diastolic dysfunction predominated. In acute myocarditis due to cardiotropic viral pathogens, Escher et at (37) have shown that 90% of the patients recover early with normal ejection fraction. However on follow up after 4-6 years they develop significant diastolic dysfunction.

Identification of the presence of diastolic dysfunction and gauging its severity is useful in the optimization of the volume status and hemodynamic parameters. Different composite indices are used to assess the diastolic function. These indices are:

1. Mitral annulus velocities on tissue Doppler: E/e' ratio

2. Mitral inflow patterns: E/A, deceleration time, IVRT (IsoVolumic Relaxation Time)

3. Pulmonary venous inflow patterns

Mitral inflow patterns - E/A ratio

The blood flow from the left atrium to left ventricle occurs in 3 stages. The E wave is caused by the initial rush of blood, when the valve opens causing a peak velocity in early diastole. A period of low or no flow occurs after this which is known as diastasis. The A wave occurs in end- diastole when the contraction of atrium causes a final rush of blood into the ventricle. Studying the movement of the anterior mitral leaflet in M-mode is the best way to assess these parameters; and is best done with Pulsed wave Doppler (PWD). In the apical 2 or 4 chamber view the PWD cursor is placed, between the tips of the open mitral leaflets.

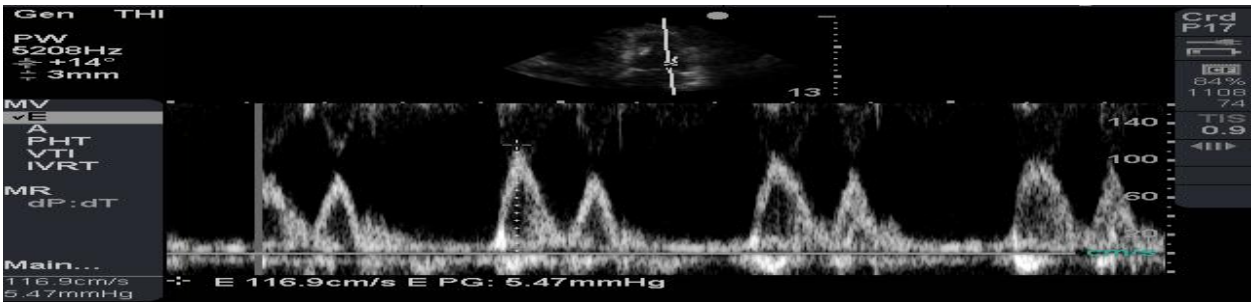


Figure 3 Mitral valve inflow patterns – Normal Inflow pattern

The mitral inflow wave patterns are obtained on PWD and image is frozen. The E wave velocity is obtained by measuring the height of E wave, which is done after selecting "E" under "mitral valve" in the calculations menu.

The E/A ratio is calculated automatically by most echo machines.

This is summarized in Figure 5 and 6.

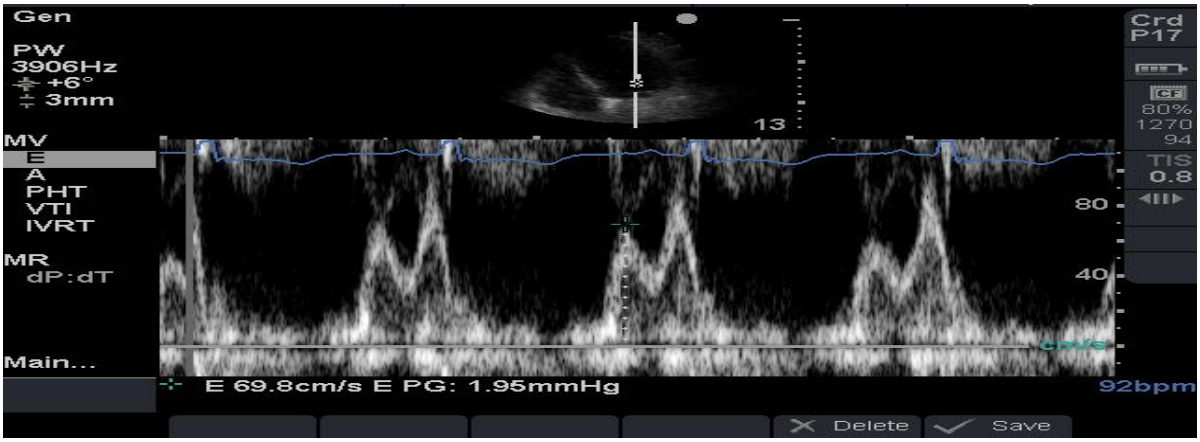


Figure 4 – MEASUREMENT OF THE E VELOCITY

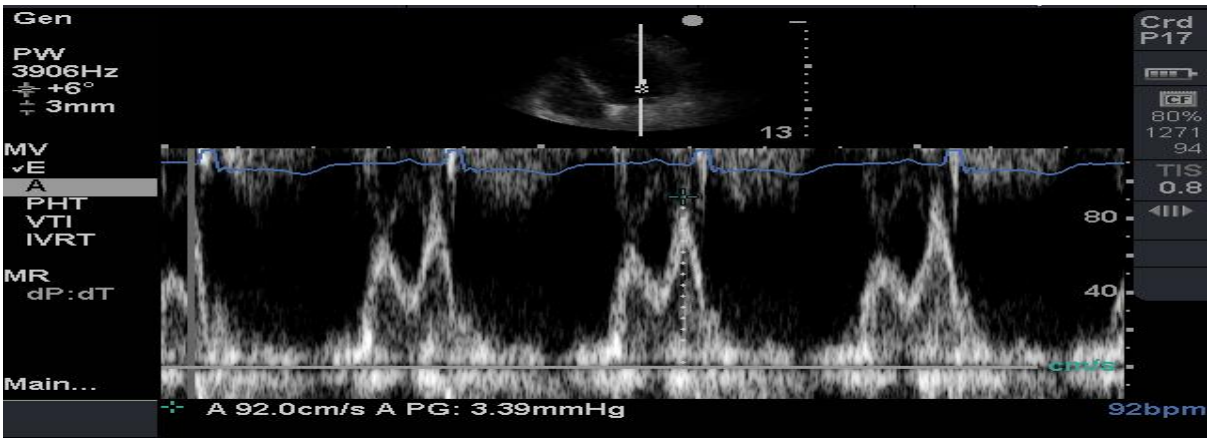


Figure 5 - MEASUREMENT OF A VELOCITY

DECELERATION TIME (DCT)

The wave pattern of mitral inflow is obtained.DCT is selected under the “Mitral Valve” from the calculations menu. The cursor is placed on the peak of E wave. On pressing select, a cursor point will appear which is then connected to the first line. Following this the cursor point is pulled to the bottom line (base).The line which joined the two points will align itself, with the down slope of E wave. The machine will now automatically calculate the deceleration

time.

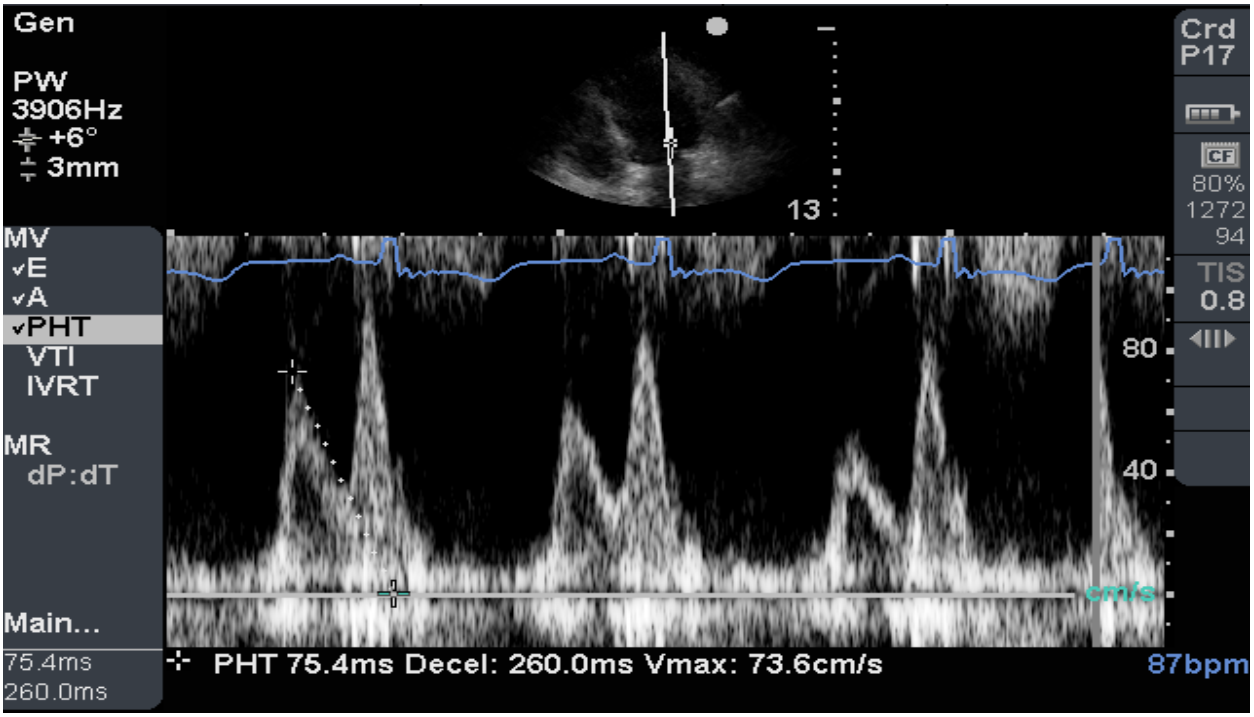


Figure 6 – DECELERATION TIME- Marking the slope of E wave to measure DCT

Mitral annular Velocity - E/e' ratio

By applying the tissue Doppler, the peak velocities of the mitral annulus in diastole are measured. It is done both both medially and laterally. These velocities are marked as e' (medial) and e' (lateral).After acquiring the A4C view, PWD is selected. Tissue Doppler imaging (TDI) is switched on. In the base of mitral leaflet over the medial mitral annulus, a sample volume of 2-mm to 5-mm is placed.

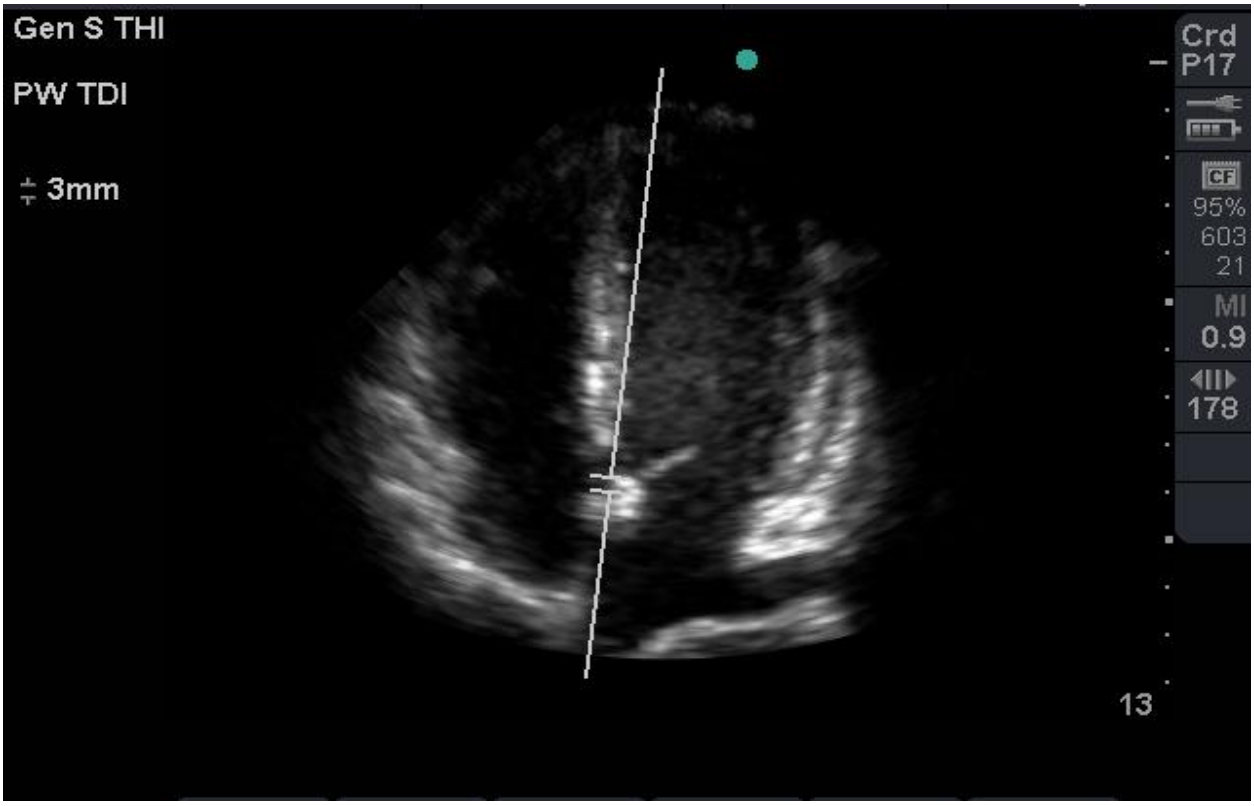


Figure 7 MEASUREMENT OF E/e' - TDI cursor placed on the medial mitral annulus

In diastolic phase 2 negative waves and in systolic phase 1 positive wave is seen. The first wave of diastole is because of the movement of the mitral valve annulus towards the left atrium which occurs during the initial filling phase of the left ventricle. This wave is called as e'. The second wave of diastole is called as a'. The systolic wave is labeled s'.

After acquiring the waveform by freezing the screen, "e' (medial)" under "TDI" which is seen in the calculations menu is selected. The peak e' velocity is measured with the cursor.

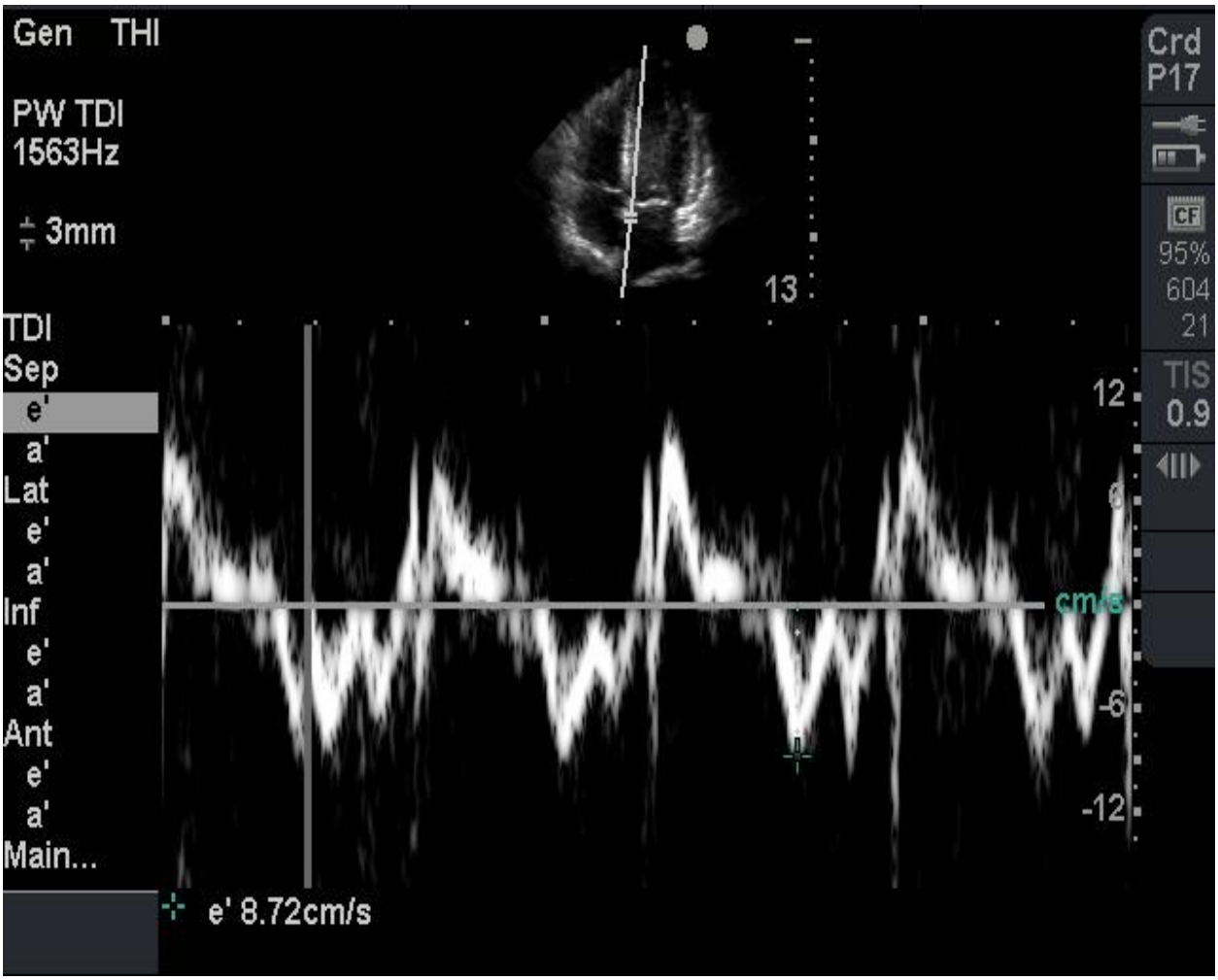


Figure 8- Measurement of e' on the medial annulus tissue Doppler trace

GRADING OF DIASTOLIC DYSFUNCTION

Grade 1: Normal filling pressures with impaired relaxation

Grade 1a: Elevated filling pressure with impaired relaxation pattern.

Grade 2: Pseudo normalized pattern

Grade 3: Restrictive pattern with reversibility

Grade 4: Irreversible restrictive pattern

Grade 1 diastolic dysfunction (Impaired myocardial relaxation)

The first abnormality in diastolic dysfunction, due to any cause, is the decrease in myocardial relaxation. The common causes are left ventricular hypertrophy, increasing age and myocardial ischemia. The Dct (>240 sec) is prolonged with E/A ratio < 1. In tissue Doppler assessment, the E/e' ratio (medial) <8, with reduced e' suggesting a normal LA pressure. The wave of pulmonary venous inflow called D wave has small amplitude than S wave. The AR wave is normal.

Grade 1a diastolic dysfunction (Impaired myocardial relaxation with elevated filling pressures)

The pattern resembles Grade 1.However E/e' ratio (medial) is > 15, suggestive of a high LA pressure.

Grade 2 diastolic dysfunction (Pseudo normalized pattern)

Deterioration of the diastolic LV function causes a decrease in LV compliance leading to increase of LA pressure as well as the diastolic filling pressure. The E wave velocity in the transmitral part increases progressively which causes decrease in Dct. As it happens, it goes through a stage which simulates a normal filling pattern causing E/A ratio to vary between 1 and 2 and the Dct between 160 and 240ms.This is called as pseudo-normal pattern, which is a pattern of transition from improper relaxation to restrictive filling. This is a resultant effect of increased LA pressure superadded on a relaxation abnormality.

The following clues help to differentiate this from a normal filling pattern

1) Pulmonary venous flow AR >25cm/sec, and greater than transmitral A wave.

2) E/e' ratio (medial) >15.

3) Presence of LA enlargement or LV hypertrophy.

Grade 3 and 4 diastolic dysfunction (restrictive pattern)

As the severity of diastolic dysfunction increases, the compliance of left ventricle reduces and LA pressures increases. The low compliance of the LV leads to a fast increase in the early Left ventricular pressure. This causes shortening of the inflow and deceleration time. The Dct is < 160ms and E/A ratio is > 2.The high LA pressure leads to an E/e' ratio >15 at the medial annulus. A flow reversal occurs in pulmonary vein as the forward diastolic pulmonary vein flow stops in mid-late diastole and during atrial contraction, leading to a prolonged AR.

Reduction of preload by performing Valsalva maneuver or by administration of nitroglycerine leads to a reversal to grade 1 or 2, which indicates that there is reversibility of the cardiac restriction and is termed as grade 3.

If this reversal is absent, diastolic filling becomes irreversible (grade 4).

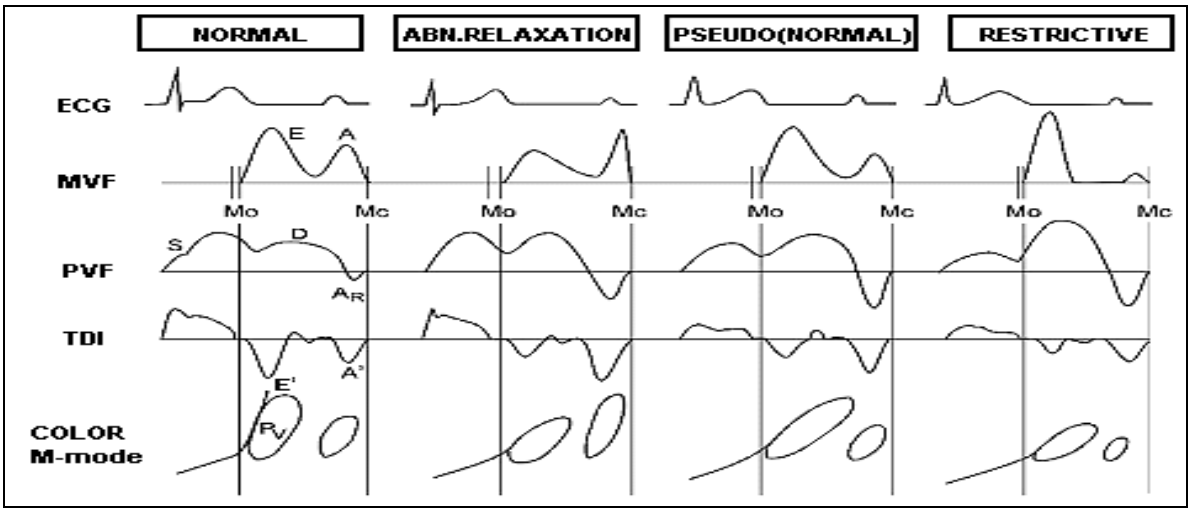


Figure 9 - Representation the different diastolic filling patterns

http://www.fac.org.ar/scvc/llave/echo/roeland/roelandi.htm

Left atrial pressure (LAP)

Elevation of left atrial filling pressures is a characteristic of heart failure. In order to optimize therapy in management of cardiac failure and to predict prognosis as well as to assess disease status at follow up, determination of LAP is required. Pulsed wave Doppler echocardiography is an effective practical tool for non-invasive assessment of left atrial pressures.

In patients with atrial fibrillation, cardiac allograft, sinus tachycardia as well as in normal subjects, E/e' ratio has been applied successfully to estimate left ventricular filling pressures. An E/e >10 estimates a pulmonary wedge pressure of > 12mm of Hg(38). A E/e <8 indicates normal pressure and E/e >15 implies high pulmonary wedge pressure (39).

The formula to calculate LA pressure:

Sinus rhythm- 2+1.2(E/e')

Sinus tachycardia -1.5+1.5(E/e')

Atrial fibrillation - 6.5+0.8(E/e')

The E/e' is obtained from the medial mitral annulus.

Assessment of LV systolic function

Ejection fraction [EF]

The end diastolic left ventricular volume (LV) in percentage, measured as the volume which is ejected from left ventricle during contraction(systole) is called as Left ventricular ejection fraction (LVEF).50% and above is considered normal. This is used as an indicator of LV systolic function (contractility).The common methods used to assess EF are the M-mode, 2-D and the 3-D echocardiography.

M-mode LV dimensional method

In M mode echocardiography, the EF is measured as a percentage which is obtained from the middle part of left ventricular diameters. This is measured in end of diastole and systole. It is noted as fractional shortening or LV shortening. In the parasternal long axis (PLAX) view, a M-mode cursor is kept over the septal and posterior LV walls, which is on the tip of the mitral leaflets. In the M-mode measurements, the internal dimensions of RV, thickness of inter - ventricular septum, internal LV dimension and LV thickness of the posterior wall at end-diastole (timed on ECG or largest LV internal dimension) and at end-systole (ECG timed or smallest LV internal dimension) are taken.

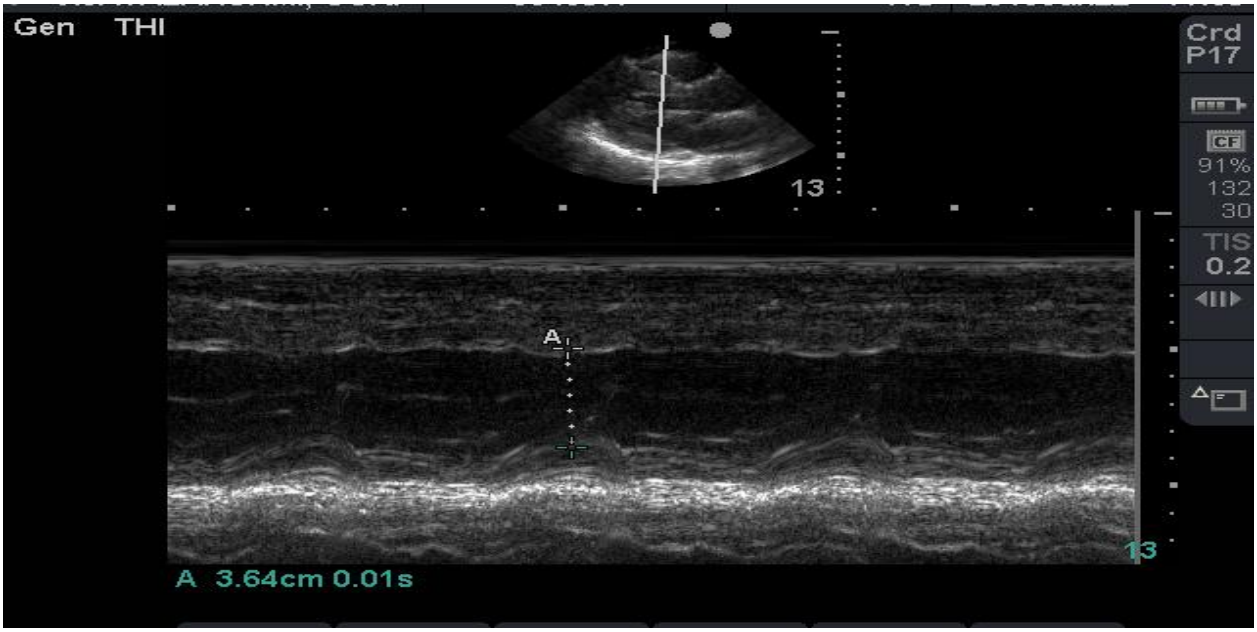


Figure 10 - Systolic measurement in parasternal long axis (PLAX) view

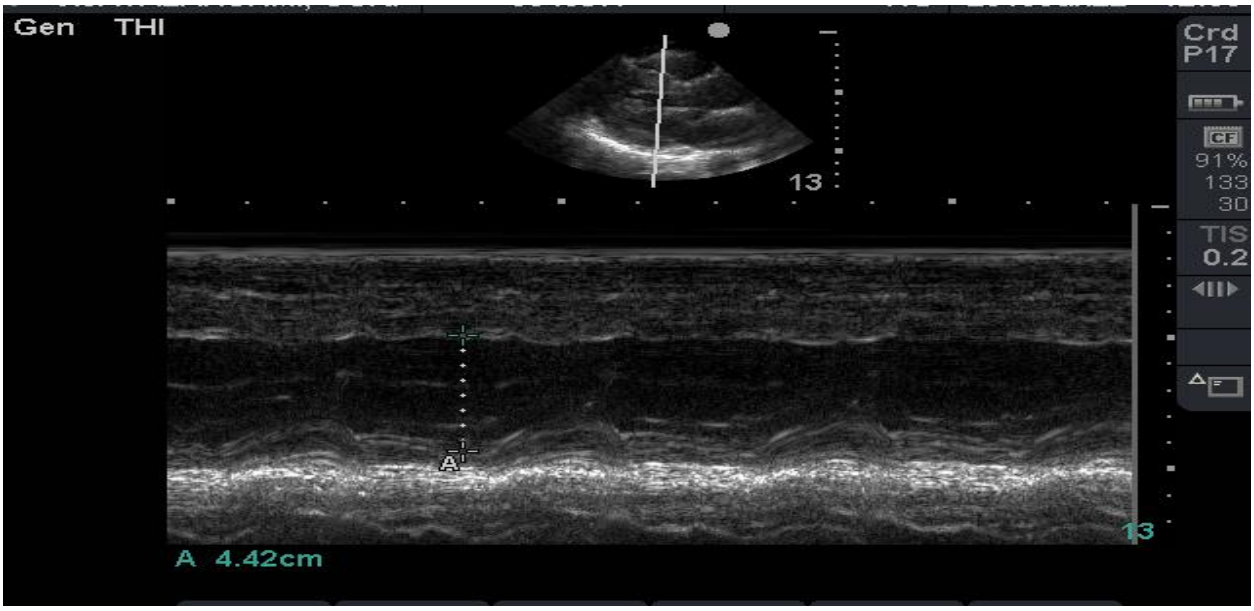


Figure 11- Diastolic measurement in parasternal long axis (PLAX) view

Machines will derive the ejection fraction and fractional shortening based on the measurements. The difference between the left ventricular end diastolic diameter (LVEDd) and the left

ventricular end systolic diameter (LVESd) over LVEDd is called fractional shortening which is expressed as a percentage. The normal value ranges between 30% to 45%.

"Cubed" or "Teichholtz" equations uses derived volumes which can be used to calculate ejection fraction:

Cubed equation - V m3 = D3 where:

V m3= volume (cm3) from cubed M-mode calculation D = M-mode LV dimension (cm)

Teichholz formula: V mt = [(7.0/2.4)+D] (D3)

[V mt = volume (cm3) from M-mode Teichholz calculation]

In a diseased ventricle, the usefulness of this is limited in view of the multiple geometric assumptions. In dilated and spherical ventricles, there is a potential over estimation of left ventricular volumes because the ratio of long to short axis in the ventricle increases.

The derived formula by Teichholz compensates for ventricles with size abnormality but only in the absence of regional wall motion abnormalities. The normal ejection fraction in M mode ranges betweens 50% to 75%.

There are multiple drawbacks in EF calculation using the M-mode. The M-mode assessment provides contractility assessment along a single line. In a patient with ischemic heart disease with regional wall motion abnormalities, LV dysfunction severity can be underestimated, if only a normal region is assessed or overestimated if the beam transits through the areas where regional wall motion anomalies occur.

Another potential disadvantage of the M-mode assessment is that it does not represent the true minor axis dimension. This occurs commonly in elderly patients and emphysematous patients. In

these patients there occurs angulation in the interventricular septum which leads to the M-mode beam traversing the ventricle in a tangential manner causing overestimation of the true internal dimension.

Volume status and preload responsiveness assessment

Central venous pressure (CVP) as an estimate of inferior venacava (IVC variability)

Assessment of volume status is important in guiding management of a haemodynamically unstable patient. Determination of the nature of shock is also important. Monitoring central venous pressures for assessing fluid status is currently being replaced by newer ultrasound guided techniques. Studies comparing the ultrasound techniques with central venous pressure monitoring showed a good correlation in both mechanically ventilated and non ventilated patients. This proves that ultrasound guided techniques are a better non invasive tool in assessing the volume status compared to other methods.

Echocardiography of the IVC is done using the transthoracic approach at the subcostal level. The transducer is placed below the xiphisternum at 1-2 cms to midline on the right side. The marker is kept pointing towards the notch of the sternum. A 2 dimensional image of the Inferior venacava, entering the right atrium is obtained. About 1 – 2 cms from the junction of IVC with the right atrium, an M mode line is placed and the image is obtained. The maximum and the minimum diameter of the IVC trace is obtained.

This is summarized in Figure 13.

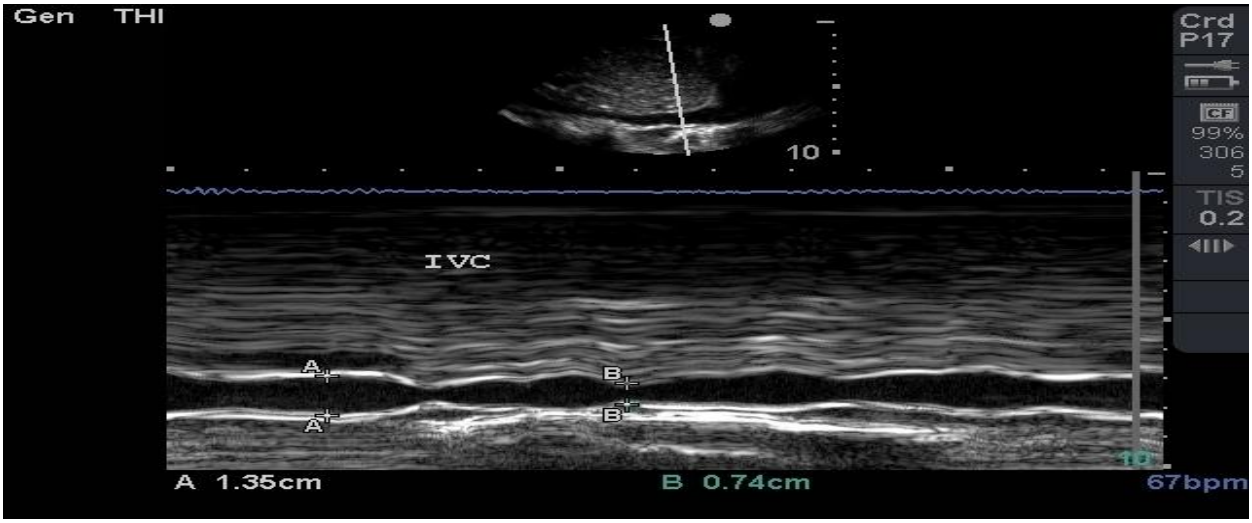


Figure 12 – Measurement of the maximum and minimum diameters in a M-mode tracing of the IVC showing marked IVC variability.

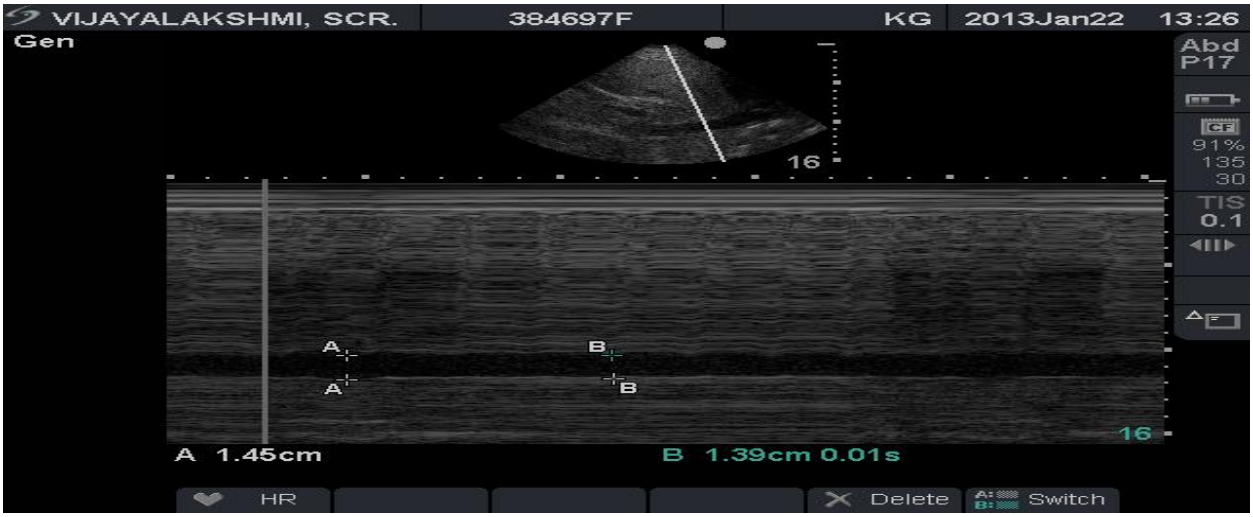


Figure 13 – Measurement of the maximum and minimum diameters in a M-mode tracing of the IVC showing insignificant IVC variability

IVC diameter

When the IVC diameter (IVCD) becomes smaller than 1 cm a low CVP value is obtained and when the diameter increases more than 2 cm, an abnormally high CVP is obtained. A wide variation however exists. With application of positive pressure ventilation the absolute

measurements are not applicable. The IVC size indicates the volume status but will not provide information on volume responsiveness, which are two different entities.

A virtual IVC is a completely collapsed IVC which is difficult to be visualized. If this occurs in a mechanically ventilated or spontaneously breathing patient, it suggests severe volume depletion with no associated absence of raised intra-abdominal pressure.

IVC collapsibility index

Studying the variation of IVC diameter in different phases of respiration will help in differentiating normal subjects from those patients who have raised right atrial pressure. In a healthy spontaneously breathing subject, variations in pleural pressure occur cyclically. This is transmitted to the right atrium which produces cyclic variations in venous return. These variations increase with inspiration causing an inspiratory decrease of about 50% in IVC diameter.

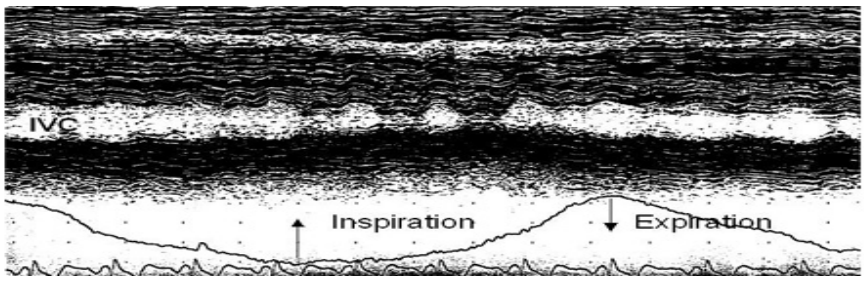


Figure 14 - IVC Variability – Normal subjects

The IVC collapsibility index is the difference between the value of the maximum and the minimum diameter. This is divided by the maximum of the two values. The maximum diameter is used as the denominator. This index is valid for spontaneously breathing patients not requiring mechanical ventilation. This can be used as an indicator of volume status (hypovolemic,

hypervolemia) and right atrial pressure; however it cannot be used as indicator of volume responsiveness. IVC Collapsibility index helps in estimation of CVP non-invasively and also has been studied as a tool to monitor fluid removal during hemodialysis and ultra filtration.

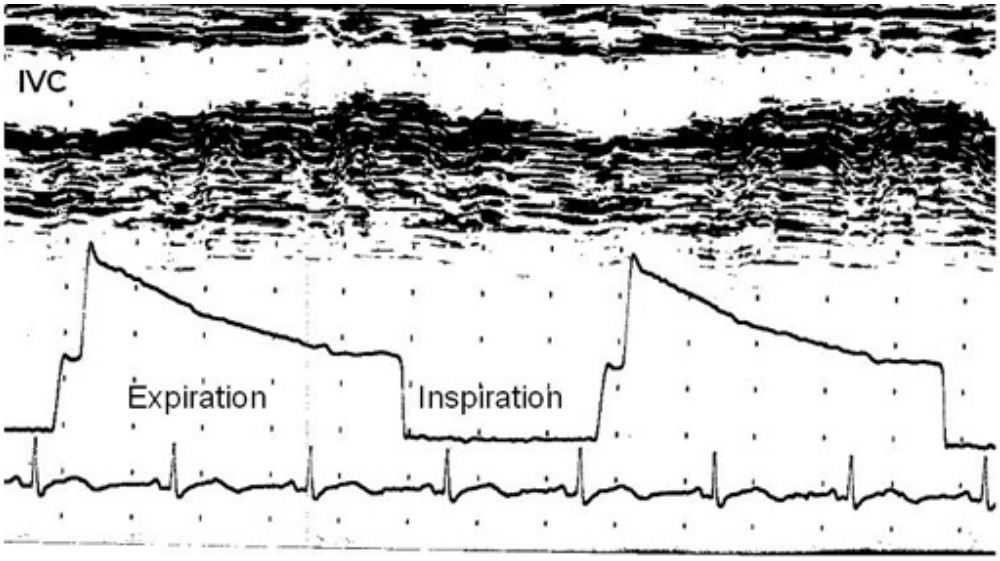


Figure 15 – IVC Variability – Ventilated patients

In a patient on mechanical ventilation, the inspiration causes the pleural pressure to increase, which is subsequently transferred to the right atrium. This in turn reduces the venous return. This leads to a reversal in the cyclic changes of the IVC diameter causing a rise in the inspiratory phase with a drop in the expiratory phase. These variations are observed only with normal right atrial pressures. In a patient with signs of hypovolemia or circulatory insufficiency more variations occur. In a patient receiving mechanical ventilation, measuring the diameter of IVC will not be an accurate predictor of the right atrial pressure and lack of respiratory variations in a patient with signs of circulatory insufficiency indicates that volume expansion will not be of benefit in 90% of the situations. ΔIVC is a quantification of this variation, calculated by

measuring the difference between the maximum and minimum diameters on the M-mode and dividing it by the mean of the two. The denominator here is the mean diameter.

In a patient on mechanical ventilation, a variation more than 12% indicates that these subjects would show response to volume expansion (filling) by means of increase in the cardiac output when compared to those who would not show any response. This has a 93% of positive predictive value with a negative predictive value of 92%. The measurements must be taken during ventilator breaths (mandatory). The tidal volume should be a minimal of 8 ml/kg and the patient should be in sinus rhythm to assess this parameter.

Distensibility index is another index, and it differs from ΔIVC in that the denominator used is the minimum diameter. The cutoff value for this index is 18%.The normal IVC variation in a spontaneously breathing patient is 50%. These two indices mentioned above are not reliable in spontaneously breathing patients.

This technique is a dynamic and a noninvasive parameter. It evaluates the benefits of volume expansion. The examination of the IVC is easy and it can be done by someone with limited experience in echocardiography.

Relating IVC measurements and CVP:

In spontaneously breathing patients:

IVC diameter	Collapse	CVP
<1.0cm	complete collapse	5 cms
1-2cms	> 50% collapse	10 cms
1-2cms	< 50% collapse	15 cms
> 2cms	0-50%	20 cms
>2cms	no change	25 cms

In ventilated patients with no spontaneous breaths:

IVC diameter	Collapse	CVP
<1.0cm	complete collapse	5 cms
1-2cms	> 18% collapse	10 cms
1-2cms	< 18% collapse	15 cms
> 2cms	0-18% change	20 cms
>2cms	no change	25 cms

4.10.5 Myocarditis in Scrub Typhus

The cardiac manifestations in scrub typhus have not been well studied. There are case reports and small case series on myocarditis complicating scrub typhus infection. Sittiwangkul et al (35) in his series of 4 patients with scrub typhus presenting with fulminant myocarditis, all 4 of them had evidence of myocarditis in the form of elevated cardiac enzymes and myocardial dysfunction (low left ventricular ejection fraction). All 4 were on multiple vasoactive supports and 2 of the 4 succumbed to the illness. Myocarditis in scrub typhus in pediatric population has been studied in south India, Kumar et al (40) in his cohort of thirty five children myocarditis was diagnosed if features of:

(i) Congestive cardiac failure or cardiomegaly

(ii)Haemodynamic compromise that required a vasopressor (≥5g/kg/min of dobutamine or dopamine)

(iii)Left ventricular dysfunction identified by echocardiography without previous cardiomyopathy

(iv) Elevated CPK-MB levels in the blood, with or without ECG abnormalities.

Hypotension was defined as a systolic blood pressure below the 5th percentile for the corresponding age, sex and height. The incidence of myocarditis in this series was 34% (40).

4.10.6 OTHER RICKETTSIAL ILLNESSES

The myocardial dysfunction has been extensively studied in patients with Rocky Mountain spotted fever (RMSF) caused by *Rickettsia rickettsia* transmitted by the ticks, endemic in south Atlantic and south American states. In patients with RMSF, enlargement of left ventricle was noted however the ventricular function was preserved. Myocarditis was a common finding at the autopsy studies. Myocardial edema was evident through increased weight of the heart, in eight of nine cases and increased volume of the interstitium, in six out of nine autopsied cases.

Rickettsia rickettsii was demonstrated in myocardium through immunofluorescent staining of myocardial capillaries, venules, and arterioles. The demonstration of the organism correlated well with the patchy distribution of interstitial mononuclear myocarditis in eight out of the nine cases. This provides the evidence of the pathogenic mechanism for vascular injury-induced myocardial edema.

5. METHODOLOGY

5.1 STUDY DESIGN

Prospective cohort study of patients admitted with scrub typhus infection.

5.2 SETTING

This study was conducted in the Christian Medical College and Hospital, a 2695 bedded teaching institute in south India. The hospitalized patients from medical wards, medical intensive care unit and medical high dependency unit were included in the study.

5.3 DURATION OF THE STUDY

The study period was for 20 months from June 2012 to January 2014 (including the two rainy seasons-the peak time for scrub typhus).

5.4 STUDY PARTICIPANTS

All adult patients admitted from accident and emergency department or from the outpatient clinic to the general medical wards, medical high dependency unit and intensive care unit with acute febrile illness. (Annexure no.1)

5.5 ELIGIBILITY CRITERIA

5.5.1 Inclusion criteria

1) Age more than 16 years.

2) Acute febrile illness (AFI) with criteria fulfilled for the diagnosis of scrub typhus.

3) Absence of any obvious focus of infection after initial clinical evaluation.

5.5.2 Exclusion criteria

1) Alternative diagnosis other than scrub typhus.

2) Patients diagnosed with autoimmune disorders.

5.5.3 Diagnostic criteria for scrub typhus

A diagnosis of scrub typhus was made on the following criteria:

1. Acute febrile illness and the presence of a positive scrub IgM ELILSA or eschar, or

2. Acute febrile illness and a positive scrub IgM ELISA seroconversion on convalescent sera, or

3. Acute febrile illness and a positive scrub IgM ELISA with other serologies negative

5.5.4 Withdrawal criteria

1. Patients unwilling to consent and further participation in the study.

5.6 OUTOME MEASURES

5.6.1 Primary outcome and definitions

The primary outcome was the number of patients with myocarditis attributable to scrub typhus infection and other causes excluded. –.

1. Myocardial injury was defined as elevation in troponin T level (more than 14pg/ml).
2. Myocardial dysfunction (left ventricular) was defined as reduced ejection fraction (less than 50%) in M mode parasternal long axis view.

3. Myocarditis was presumed when myocardial injury was associated with global myocardial dysfunction in the setting of an acute febrile illness due to scrub typhus infection.

5.6.2 Secondary outcomes

1. Mortality
2. Duration of hospital stay
3. Need for ventilation
4. Duration of ventilation
5. Use of vasoactive agents (shock)
6. Comparison of mortality and survival analysis in patients with evidence of myocarditis with patients who did not have myocarditis.

5.7 Confounders considered pre hoc

1. Pre-existing cardiac disease
2. Sepsis
3. Renal failure
4. Ventilation
5. Use of vasoactive agents

5.8 SAMPLE SIZE

Sample size calculation was based on an assumption of prevalence of myocarditis of 30% in patients with scrub typhus infection. All adult patients admitted with acute febrile illness (AFI) with criteria fulfilled for the diagnosis of scrub typhus, between June 2012 and March 2014 were included in the study and evaluated for myocarditis. The sample size required to show the

prevalence of myocarditis in scrub typhus as 30%, with 10% precision was calculated using the formula:

$$\frac{4 * p * q}{d * d}$$

$$\frac{4 * 70 * 30}{10 * 10}$$

This was calculated to be 84.

5.9 Source of information

1. Detailed clinical history and through general physical examination of the study participants
2. Study participants relatives
3. Laboratory testing
4. Echocardiography

5.10 Validation

The principal investigator underwent training in echocardiography by a trained critical care sonologist. Transthoracic echocardiography was performed with a Sonosite Micromax unit using a 1 to 5MHz phased array transducer probe. To reduce inter-observer variation in echocardiography findings, a validation study was done. Twenty patients were chosen randomly and echocardiography was done individually by the principal investigator and Dr. Kishore Pichamuthu (trained critical care sonologist) and inter-observer variation was measured using kappa and interclass correlation coefficient.

5.10.1 The Kappa Statistics

When two or more independent observers are evaluating the same variable, inter-observer variation can be measured. The calculation is based on the difference between the agreement which is actually present ("observed" agreement) compared to agreement which would be expected to be present by chance alone ("expected" agreement). Kappa is a statistic parameter which measures this difference. This is a scale standardized to lie between -1 to +1. (1 is perfect agreement and 0 is what would be expected by chance, and negative values indicate agreement less than by chance where there is systematic disagreement between the observers).

5.10.2 Interpretation of Kappa

Kappa	Agreement
< 0	Less than chance agreement
0.01-0.20	Slight agreement
0.21-0.40	Fair agreement
0.41-0.60	Moderate agreement
0.61-0.80	Substantial agreement
0.81-1.00	Almost perfect agreement

Table 1 INTERPRETATION OF KAPPA

Table 2 showing validation study on 20 patients, for binary variable Kappa was used to measure degree of agreement and for quantitative variables interclass correlation coefficient was used to determine the degree of agreement.

Variable	Kappa value	Interclass correlation coefficient
Regional wall motion abnormality #	0.57	-
Left ventricular ejection fraction *	-	0.76
E/a *	-	0.86
Left ventricular outflow tract *	-	0.87
IVC variability *	-	0.76
E/e' *	-	0.88

E/A- mitral valve annulus measured in apical 4 chamber view, E/e'- medial mitral valve annulus measured using tissue Doppler, IVC- inferior venacava.
- binary variable, hence kappa value used.
* - quantitative variable, hence interclass correlation coefficient.

Table 2 STUDY VALIDATION

5.11 Data collection

A proforma (Annexure 2) was made containing all data required for analysis. This was filled by the principal investigator on the day of admission and updated daily till discharge from the hospital or till the patient expired. The proforma enclosed contained all data required for analysis including the echocardiography parameters. The collected data was entered in Microsoft excel spread sheet which was password protected. The data was collected in the following categories specifically.

5.11.1 Non cardiac parameters

1. Baseline demographics: age, gender, hospital number, height, weight (where feasible), place and duration of illness.
2. Co-morbid illness: diabetes mellitus, hypertension, coronary artery disease, valvular heart disease, smoking, alcohol consumption, autoimmune condition and chronic immunosuppressant use.
3. Symptomatology: presence of fever, cough, dyspnoea, myalgia and altered sensorium.
4. Laboratory parameters: creatinine, total and differential WBC counts, platelets count and blood lactate.
5. Variables necessary for computing SOFA score and APACHE II score.
6. Use of different vasoactive agents
7. Ventilation parameters: need for ventilation, type of ventilation and duration of ventilation.
8. Duration of hospital stay
9. ICU and hospital outcome

5.11.2 Cardiac parameters

1) Electrocardiography: Arrhythmias (sinus tachycardia or bradycardia, other supraventricular and ventricular arrhythmias), ST-T changes, QRS abnormalities

2) Cardiac enzymes: CKMB and troponin T were used as specific cardiac biomarkers of myocardial injury

3) Echocardiogram: To assess cardiac function (left and right ventricular), regional wall motion abnormalities, measure of filling status (refer table 3)

5.11.3 Derived variables from ECHO parameters

Systolic function of the heart was assessed by using cardiac index, ejection fraction (EF) and the stroke volume index (SVI). EF was calculated in the parasternal long axis view by using the M mode.

The left ventricular outflow diameter was obtained using the parasternal long axis view and the velocity of the outflow tract was measured at the left ventricular outflow tract using Doppler probe in the apical 5 chamber view. The cardiac index and SVI were determined with these parameters.

Left ventricular systolic dysfunction was diagnosed in patients with EF less than 50%.

Diastolic dysfunction was diagnosed in patients with E/A lower than 1, and in patients with diastolic dysfunction an E/e’ lower than 15 was considered as mild diastolic dysfunction and more than 15 was considered as severe diastolic dysfunction.

CARDIAC VARIABLES MEASURED BY ECHOCARDIOGRAPHY

Stroke volume index (SVI)	Cardiac index/heart rate ml/beat.m2
Cardiac index (CI)	Cardiac output/ BSA
Cardiac output (CO)	Stroke volume x heart rate
Stroke volume (SV)	$0.785 \times D^2 \times VTI$
left ventricular stroke volume index (LVSVI)	(MAP-LAP)* SVI *0.0136 gm.m/m2/beat
Systemic Vascular Resistance Index (SVRI)	((Map-CVP)/CARDIAC OUTPUT)*80 dyne.sec/cm
Left Atrial Pressure (LAP)	In sinus rhythm: 2+1.2(E/e') Sinus tachycardia: 1.5+ 1.5(E/e') Atrial fibrillation: 6.5 + 0.8(E/e')

D-left ventricular outflow tract diameter, VTI-velocity time integral, measured in the LVOT proximal to the aortic valve, BSA- basal surface area.

Table 3 CARDIAC VARIABLES MEASURED BY ECHOCARDIOGRAPHY

ASSESSMENT OF QUANTITATIVE VARIABLES	
Quantitative variable under study	Analysis
APACHE II Score on admission	Calculated on enrolment
SOFA Score	Calculated on enrolment
Duration of fever	Necessary for estimation of duration of infection
Vital signs (heart rate, temperature, blood pressure, respiratory rate.)	Necessary for calculation of APACHE II and SOFA score
Liver function test, PT and albumin	Necessary for calculation of SOFA score and evaluation of liver function
Creatinine, sodium, potassium, urea	Necessary for calculation of SOFA score and evaluation of renal function
Arterial pH, pO2, pCo2	Necessary for calculation of APACHE and SOFA score
Haemoglobin, total counts, platelet counts.	Necessary for calculation of APACHE II and SOFA Score and for evaluation of haematological function
Vasoactive agent use	Necessary for calculation of vasopressor score and SOFA score
CKMB, Troponin T	Necessary for evaluation of cardiac involvement
Echocardiography findings(LVEF, CI, E/e', LAP)	Necessary for evaluation of cardiac dysfunction

Table 4 ASSESSMENT OF QUANTITATIVE VARIABLES

5.12 STATISTICAL METHODS

Statistical analysis was done using SPSS version 15 and Stata 11® statistical package (Statacorp, college station, Texas, USA). Descriptive statistics were obtained for all variables in the study. Categorical and continuous variables were compared for outcome by using the fisher's exact test and student t test respectively. All continuous data were expressed as mean ± SD unless the data was not normally distributed. A p value of < 0.05 was considered statistically significant for all analysis. The presence of myocarditis, myocardial injury and dysfunction were correlated with mortality. This was expressed as odds ratio (OR) with 95% confidence interval (CI). A multivariate logistic regression analysis was performed to assess and identify those factors which were independently associated with myocarditis.

5.13 FUNDING

Fluid research grant, Christian Medical College

5.14 INSTITUTIONAL RESEARCH BOARD APPROVAL AND ETHICAL CONSIDERATIONS*:*

In this observational cohort study there were no ethical issues. The study was explained to the participants/relatives and a written and informed consent was obtained before measuring cardiac enzymes and echocardiography. Institutional Research Board (IRB) approval was obtained (IRB Min. No. 8104 dated 05.12.2012).

6. RESULTS

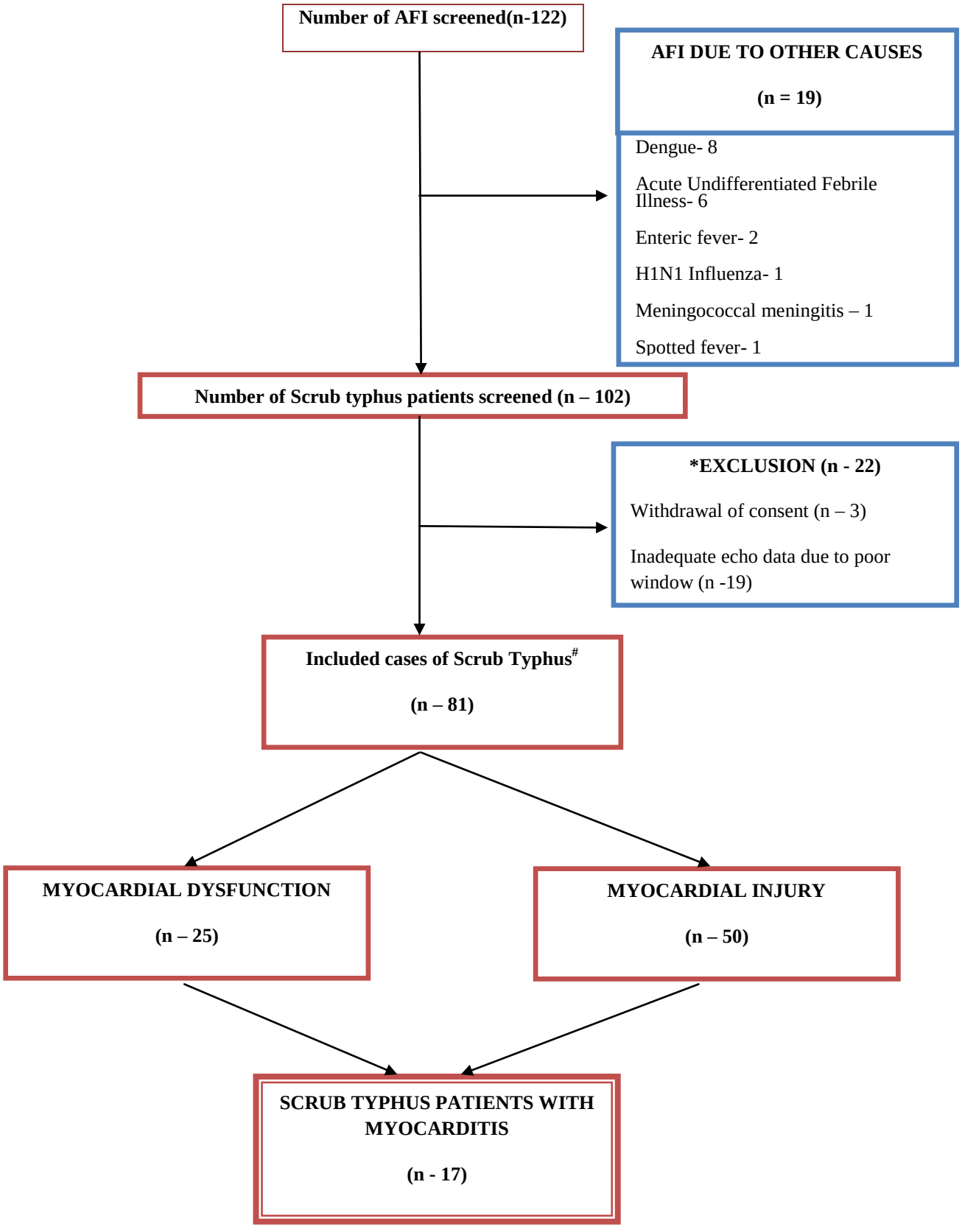
6.1 PARTICIPANTS

This prospective cohort study was conducted over a period of 20 months (June 2012 to January 2014) in a teaching institution in South India.

Acute febrile illness due to various causes is most commonly seen during the months of rainy season in south India.

One hundred and twenty two patients with acute febrile illness who fulfilled the inclusion criteria were screened for myocarditis. On further evaluation and on using the diagnostic criteria, 19 patients were excluded as they had other etiologies for their febrile illness, 8 patients were diagnosed with dengue, 6 were diagnosed as undifferentiated febrile illness, 2 patients had enteric fever, and spotted fever, H1N1 infection and menigococcal menigitis were diagnosed in the other three patients. Twenty-two patients who were diagnosed as scrub typhus were excluded, of which 19 patients were excluded due to poor echo widow resulting in inadequate echocardiography data and 3 patients were excluded due to refusal to consent for the study. The remaining 81 patients diagnosed with scrub typhus were followed up till discharge / death for further analysis.

6.2 STUDY FLOW CHART



6.3 PATIENT DEMOGRAPHICS

The study cohort comprised of 81 patients with a mean ± SD age of 49.41 ± 16.07 and presenting at 8.11 ± 3.11 days of illness.

The study population represented scrub typhus patients from south India, predominately from Tamil Nadu (65%) followed by Andhra Pradesh (35%).

There was a slight female predominance observed, with female: male ratio of 1.3:1.

Table 5 BASELINE CHARACTERISTICS

BASELINE CHARACTERISTICS OF THE STUDY PARTICIPANTS (N-81)

Variable	Value
Age, mean ± SD years	49.41 ± 16.07
Gender ratio (female/male)	46:35
Day of presentation from onset of illness, mean ± SD) days	8.11 ± 3.11
State wise distribution, number (%)	
Tamil Nadu	53 (65.4)
Andhra Pradesh	28 (34.6)

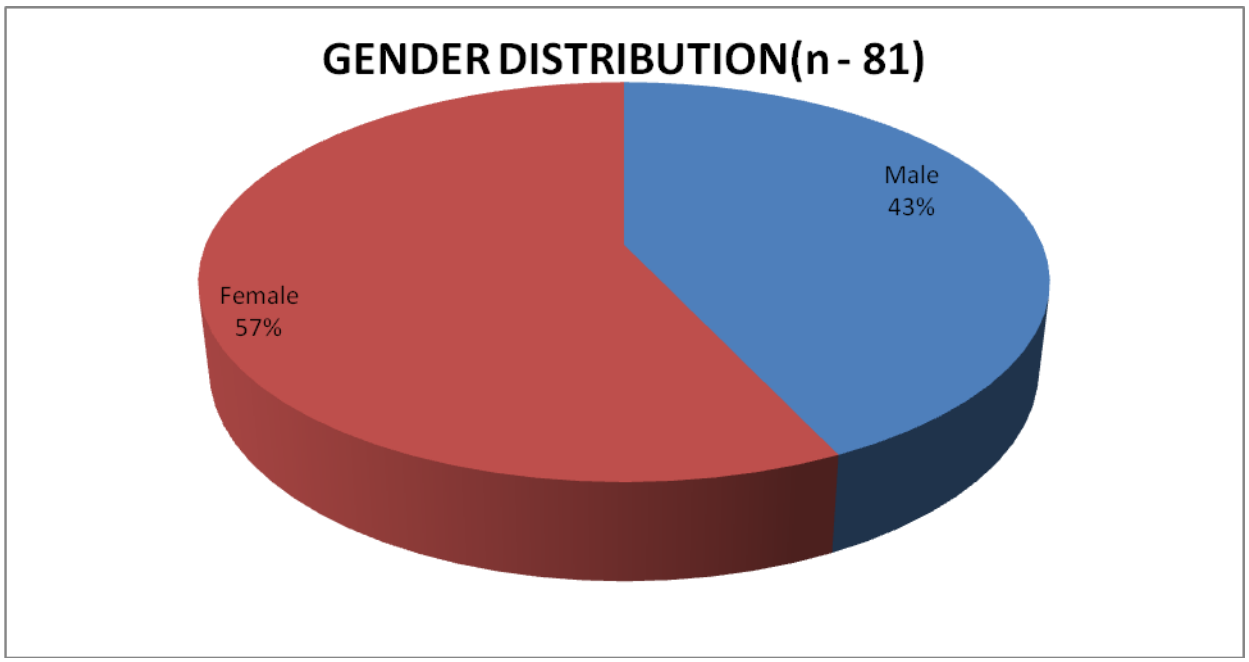


Figure 16- GENDER DISTRIBUTION OF SCRUB TYPHUS

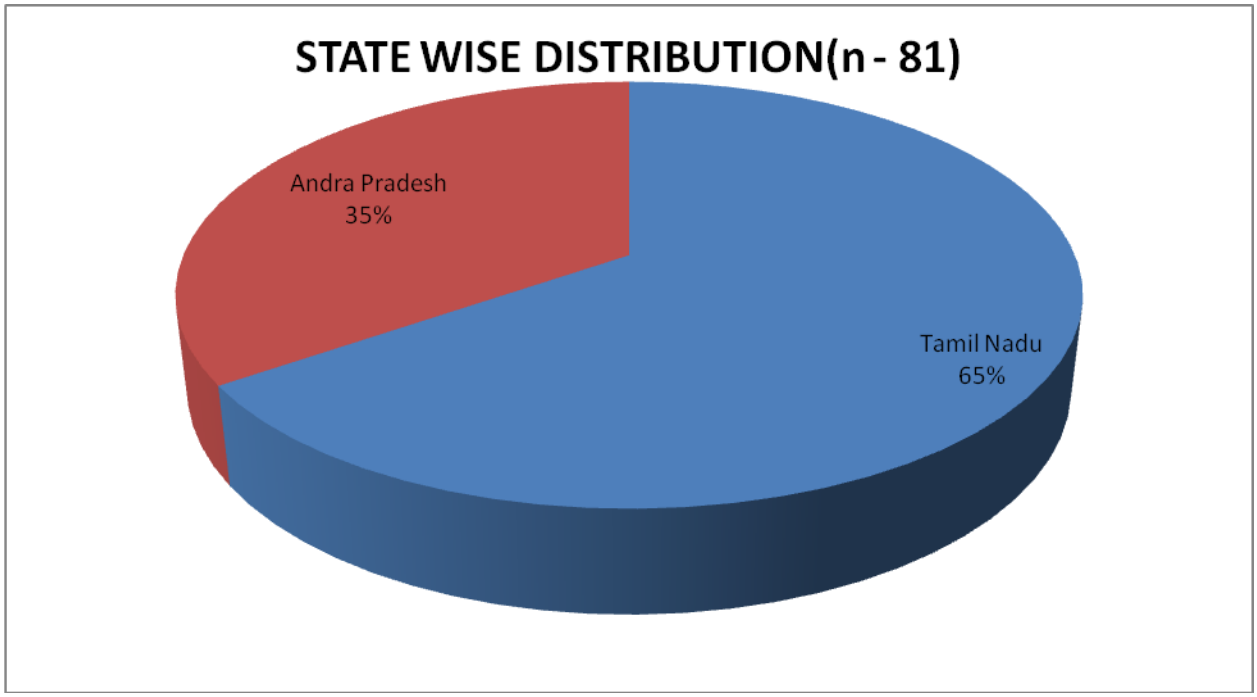


Figure 17 – STATEWISE DISTRIBUTION OF SCRUB TYPHUS

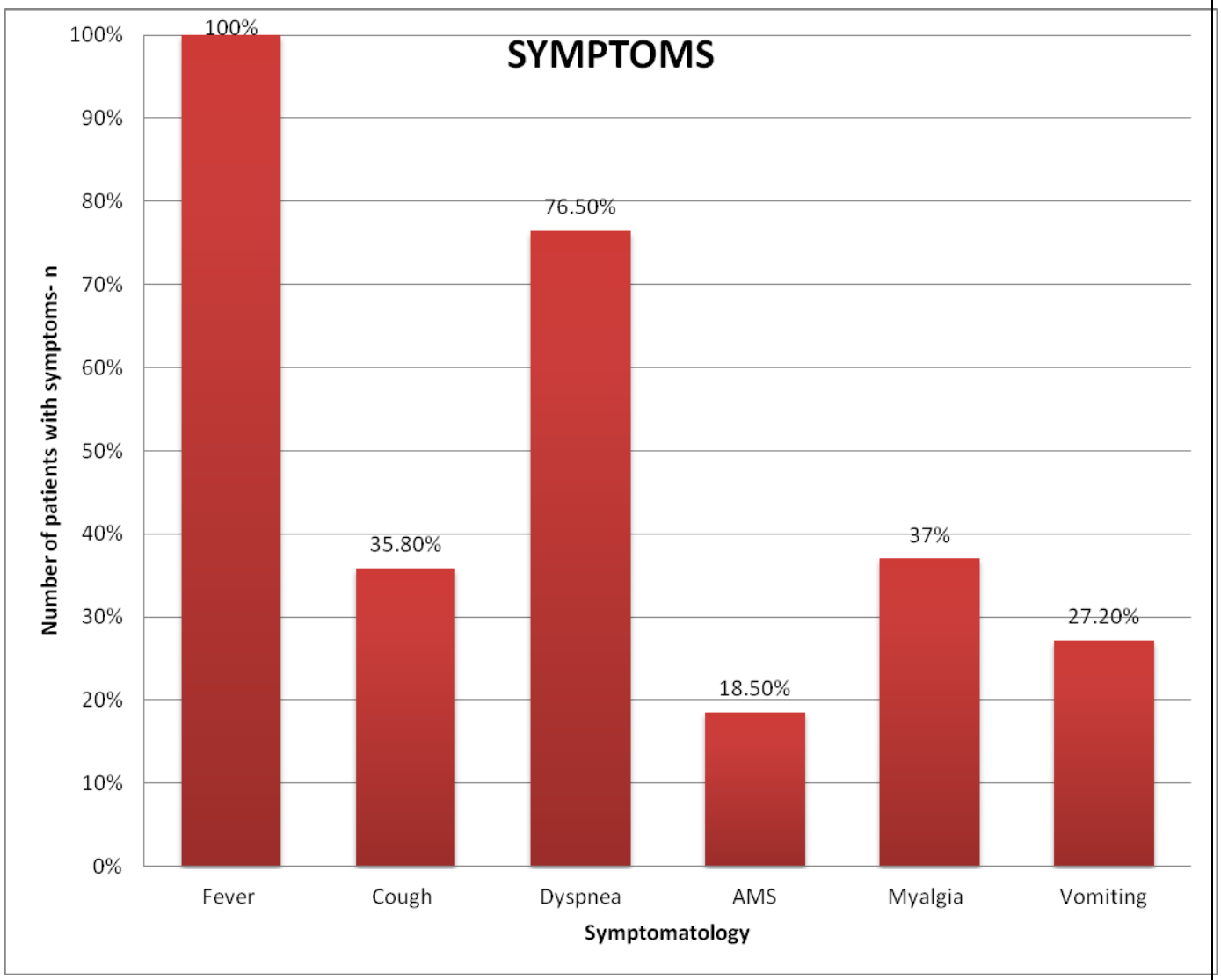
6.4 SYMPTOMATOLOGY OF PARTICIPANTS

All patients in the cohort had fever as the presenting complaint, followed by dyspnea which was seen in 52(76.5%) patients followed by myalgia in 30 (37%) patients and cough in 29 (35.8%) patients. Vomiting and altered sensorium were less commonly seen in this cohort of patients (27.2% and 18.5% respectively).

Table 6 – SYMPTOMATOLOGY OF PATIENTS WITH SCRUB TYPHUS

SYMPTOMATOLOGY OF PATIENTS WITH SCRUB TYPHUS (n-81)	
Variable	Frequency- n (%)
Fever	81 (100)
Cough	29 (35.8)
Breathlessness	52 (76.5)
Altered mental status	15 (18.5)
Myalgia	30 (37)
Vomiting	22 (27.2)

Figure 18 – SYMPTOM PROFILE OF PATIENTS WITH SCRUB TYPHUS



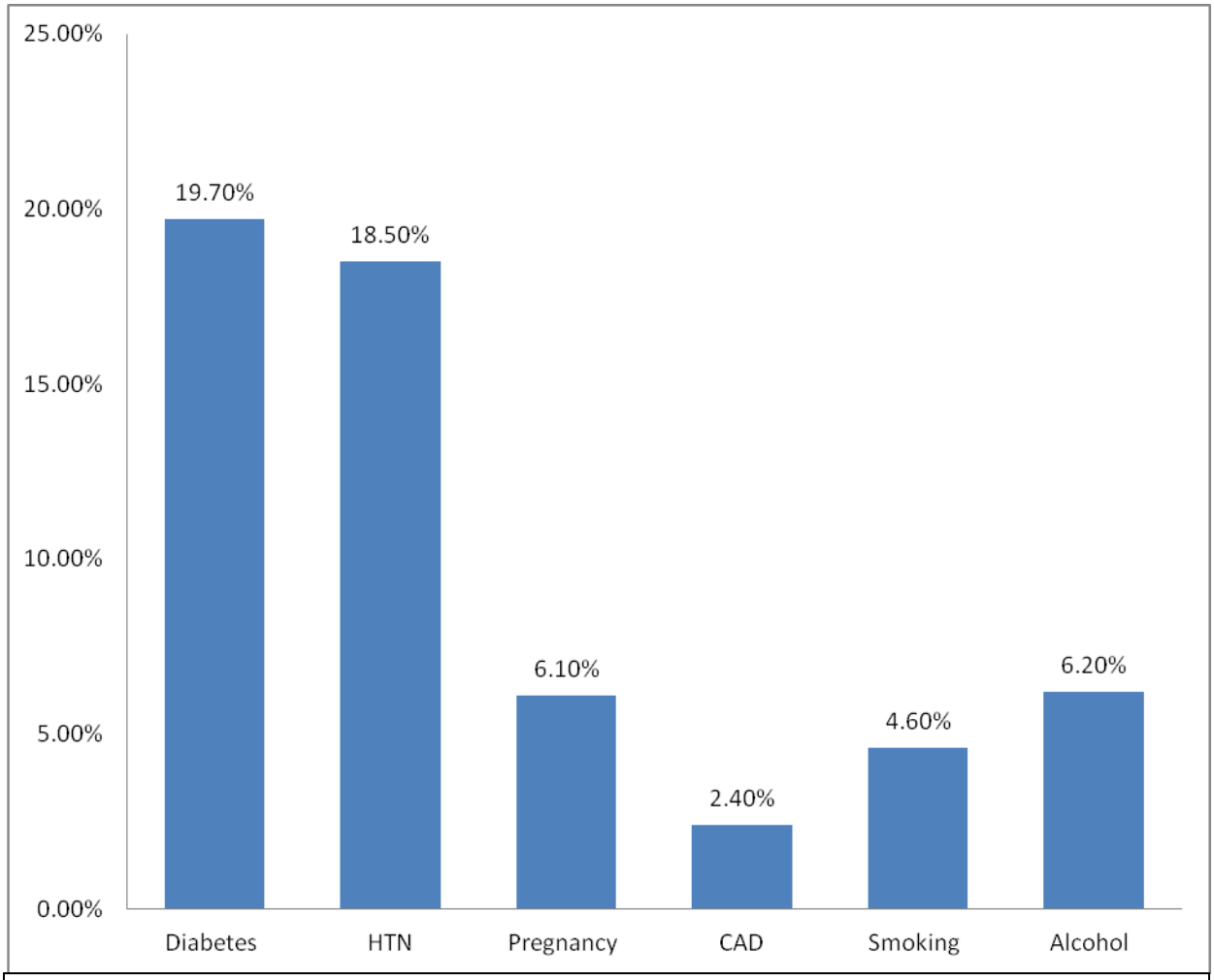
6.5 CO-MORBID ILLNESS IN PARTICIPANTS:

The underlying co-morbid illness are summarized below, Diabetes mellitus was the most common co-morbid condition which was seen in nearly one fifth of the study population (n-19), followed by hypertension seen in 15 (18.5%) patients. Five patients were pregnant and two had coronary artery disease. The number of patients with smoking and alcohol consumption was relatively low in the study group (3 and 4 patients respectively). There was one patient each with HIV infection and dyslipidemia. There was no patient in this entire cohort with history of autoimmune condition, long term immunosuppressive therapy, and hematological malignancy or platelet disorders.

Table 7 COMORBID ILLNESSES IN PATIENTS WITH SCRUB TYPHUS

CO-MORBIDITIES IN PATIENTS WITH SCRUB TYPHUS- (n-81)	
Co-morbid illness	**Frequency (%)**
Diabetes	**16 (19.7)**
Essential hypertension	**15 (18.5)**
Pregnancy	**5 (6.1)**
Coronary artery disease	**2 (2.4)**
Smoking	**3 (4.6)**
Alcohol	**4 (6.2)**

Figure 19 – PROFILE OF COMORBID ILLNESS IN PATIENTS WITH SCRUB TYPHUS



HTN-hypertension

CAD- coronary artery disease

6.6 CLINICAL SIGNS- ESCHAR

The presence of a classical eschar is of diagnostic significance; an eschar was seen in 62 (77%) of patients. Of the 62, 61 patients were scrub IgM Elisa positive, one patient was diagnosed on the basis of an eschar alone.

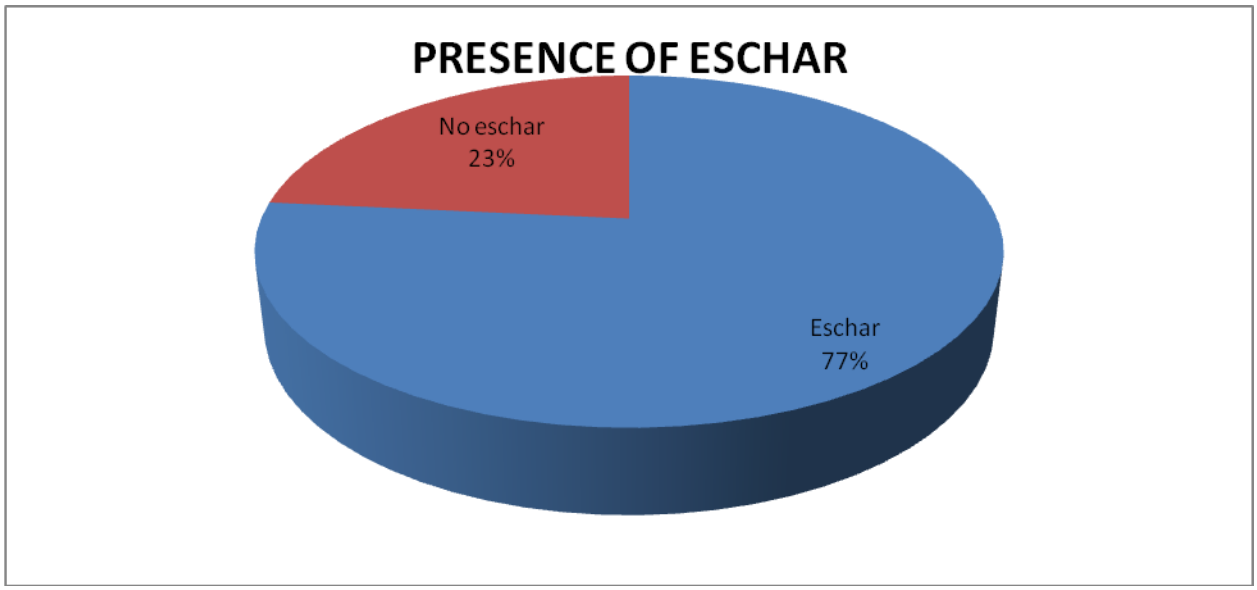


Figure 20 – PRESENCE OF ESCHAR IN PATIENTS WITH SCRUB TYPHUS

Figure 21 - ESCHAR

6.7 LABORATORY PARAMETERS

In this cohort of patients, the mean hemoglobin was 11.45 gm%. These patients had a mild elevation in their total counts with a mean of 10400 / cmm. Thrombocytopenia (platelet count less than 1.5 lakhs) was observed in 92.6% of patients with a mean platelet count of 69700/ cu mm. There was mild derangement in renal function in these patients with a mean creatinine of 1.71 mg %. The liver function test showed mild decrease in albumin, mean of 2.58 gm%. There was a mild increase in liver enzymes; both SGOT and SGTPT were elevated, mean of 139.05 and 68.65 respectively. The elevation in SGOT was more than the SGPT.

LABORATORY PARAMETERS IN PATIENTS WITH SCRUB TYPHUS (n-81)

Laboratory parameters	Mean	SD	95 % CI
Hemoglobin, gm %	11.45	2.56	4.0 - 20.4
Total counts, cmm	10400	4825.11	2700 - 30400
Platelets, cmm	69700	70372.34	4000 - 364000
Creatinine, mg %	1.71	1.43	0.4 - 8.1
Total bilirubin, mg %	2.06	1.92	0.3 - 9.6
Direct bilirubin, mg %	1.55	1.71	0 - 9.0
Serum albumin, gm %	2.58	0.58	0.5 - 4.1
SGOT, U/L	139.05	92.39	28 - 428
SGPT, U/L	68.65	49.32	10 - 366
Alkaline phosphatase, U/L	199.14	107.01	43 - 593

SGOT-Serum Glutamic –Oxaloacetic transaminase, SGPT- Serum Glutmic Pyruvic Transaminase**.**

Table 8 LABORATORY PARAMETERS IN PATIENTS WITH SCRUB TYPHUS

6.8 SCORING SYSTEM AND ORGAN DYSFUNCTION

Scrub typhus causes multiorgan dysfunction, the various organs involvement was characterized by sequential organ failure assessment (SOFA) and APACHE II score. The mean ± SD of SOFA and APACHE score were 8.94 ± 3.95 and 15.68 ± 7.01 respectively. The predicted mortality was calculated based on APACHE II score was 25.25%.

SCORING SYSTEM AND ORGAN DYSFUNCTION IN SCRUB TYPHUS (n-81)			
Scoring system	mean	SD	95% CI
SOFA score	8.94	3.95	8.06- 9.81
APACHE II score	15.68	7.01	14.13-17.23
Predicted mortality based on APACHE II	25.25	18.59	22.14-30.37
SOFA- Sequential Organ Failure Assessment, APACHE II- Acute Physiological and Chronic Health Evaluation.			

Table 9 SCORING SYSTEM AND ORGAN DYSFUNCTION IN SCRUB TYPHUS

THE SOFA SCORE:

The data on organ dysfunction was available for all the patients, the median frequency of organ involvement based on SOFA score was 4. The hematological organ dysfunction predominated with 96.3% followed by respiratory system 90.1%. Cardiovascular system involvement was seen in 62.9%, hepatic and renal involvement was present in 54.3% and 53.1% respectively. The central nervous system involvement was seen in only 18.5%.

PERCENTAGE OF DIFFERENT ORGAN INVOLVEMENT IN SCRUB TYPHUS (n-81)

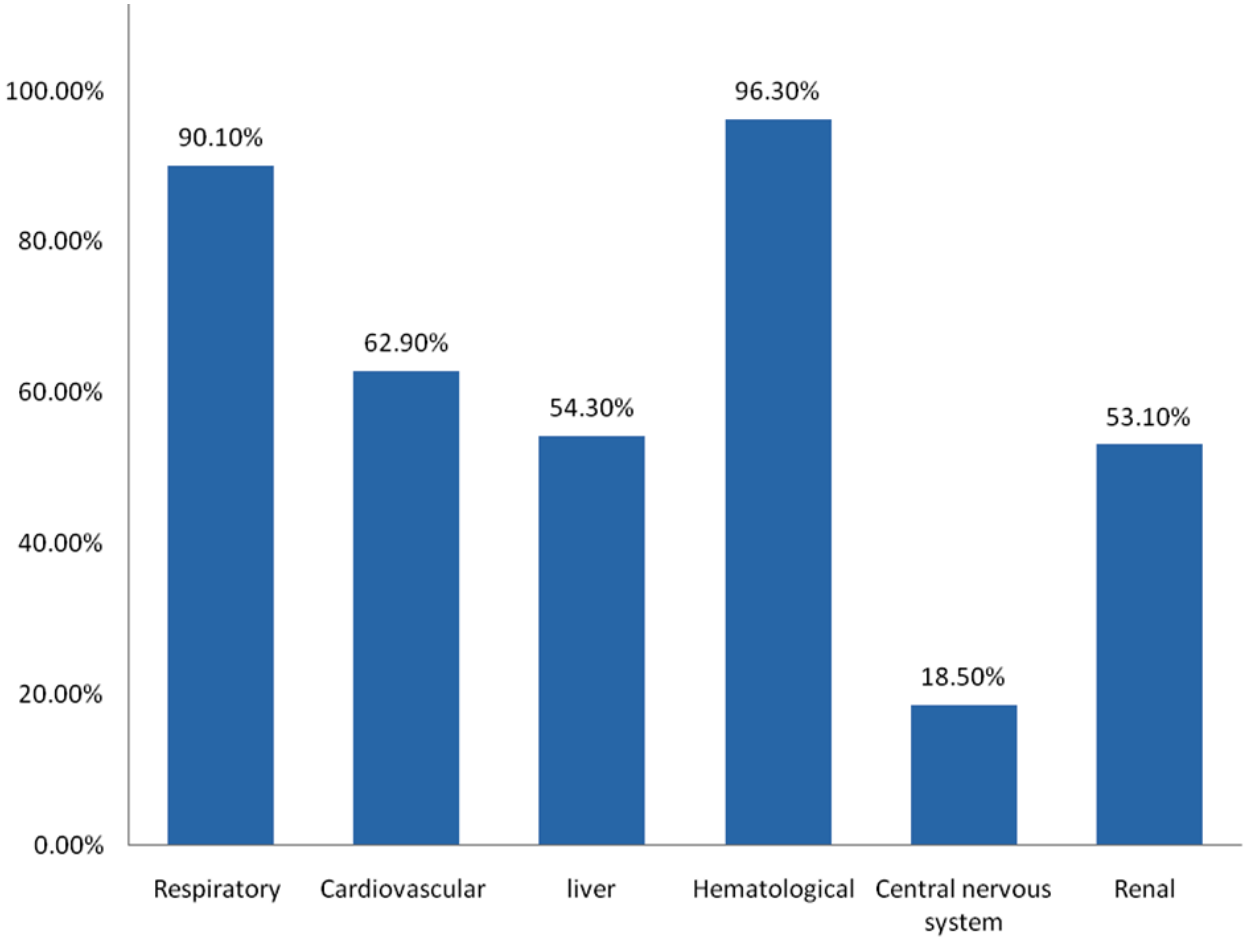


Figure 22 ORGAN DYSFUNCTION IN SCRUB TYPHUS

On the basis of SOFA score, the organ involvement was classified as organ dysfunction and organ failure. A SOFA score of 1 or 2 was considered as organ dysfunction while a score of 3 or 4 was considered as organ failure.

ORGAN SYSTEM INVOLVEMENT BASED ON SOFA SCORE (n-81)			
Organ system involved	Organ dysfunction n (%)	Organ failure n (%)	Organ involvemen n (%)
Respiratory	44 (54.32)	29 (35.80)	73 (90.1)
Cardiovascular	9 (11.11)	42 (51.85)	51 (62.9)
liver	36 (44.44)	8 (9.88)	44 (54.3)
Hematological	35 (43.21)	43 (53.09)	78 (96.3)
CNS	9 (11.11)	6 (7.41)	15 (18.5)
Renal	36 (44.44)	7 (8.64)	43 (53.1)

CNS-central nervous system, SOFA- Sequential Organ Failure Assessment.

Organ dysfunction- SOFA score 1or 2, organ failure SOFA score 3 or 4, organ involvement – SOFA score of atleast 1

Table 10 ORGAN DYSFUNCTION BASED ON SOFA SCORE

In this cohort of patients, the mean frequency of organ involvement was 4. Seven patients (8.6%) had all six organ involvement, 97.5% of them had 2 or more organ involvement.

CATEGORATION BASED ON NUMBER OF ORGAN INVOLVEMENT IN SCRUBTYPHUS		
Number of organs involved	Number of patients (%)	Cumulative percentage
One	2 (2.5)	100
Two	10 (12.3)	97.5
Three	27 (33.3)	85.2
Four	16 (19.8)	51.9
Five	19 (23.5)	32.1
Six	7 (8.6)	8.6

Table 11 CATEGORIZATION BASED ON ORGAN DYSFUNCTION

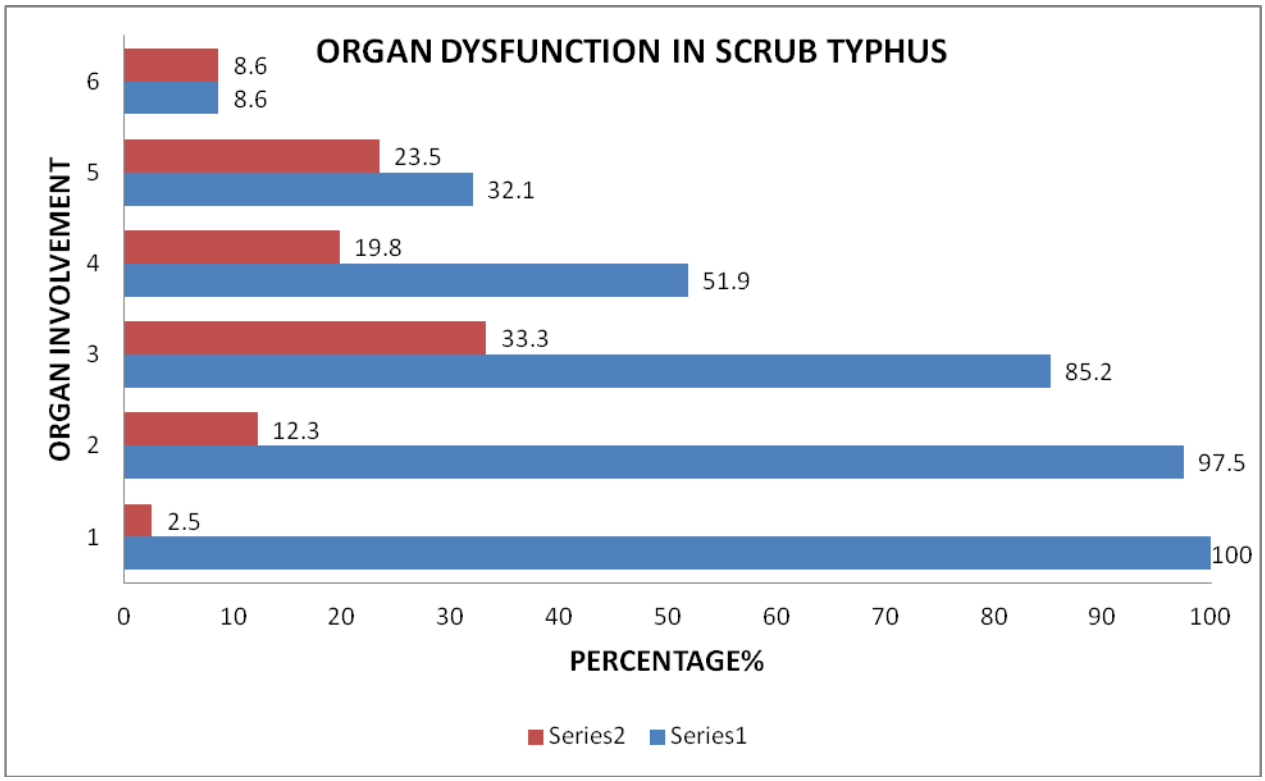


Figure 23 ORGAN DYSFUNCTION IN SCRUB TYPHUS

6.9 CARDIOVASCULAR MANIFESTATIONS

The various cardiovascular manifestations in scrub typhus were studied using the following variables:

6.9.1 Cardiac enzymes

The cardiac enzymes, CKMB and troponin T were done for all participants within forty eight hours of admission. The mean ± SD of CK-MB and troponin T of the entire cohort were 6.69 ± 9.4 and 83.1 ± 212.2 respectively.

6.9.2 Echocardiography

Transthoracic echo was performed on all participants. The mean ± SD LVEF was 57.59 ± 14.16. The mean cardiac output was 4.37 ± 1.38 liters. The cardiac index and systemic vascular resistance were measured only on 65 patients, the mean ± SD were 2.65 ± 0.89 and 2363.47 ± 949.35 respectively. The variables used to assess diastolic dysfunction, the mean (SD) of E/A and E/e' was 1.16 ± 0.36 and 9.77 ± 3.49 respectively. The combination of the absolute diameter of the IVC and the degree of collapse was used to estimate central venous pressure (CVP), the mean CVP was 11.25 ± 5.23 cm in this cohort of patients.

CARDIOVASCULAR MANIFESTATIONS IN SCRUB TYPHUS (n-81)				
Characteristic	**Number**	**mean**	**SD**	**95 % CI**
a. Cardiac biomarkers				
CKMB	81	6.69	9.4	4.88-9.07
Troponin T	81	83.1	212.2	36.21- 130.04
b. Echocardiography findings				
LVEF	81	57.59	14.16	54.46-60.72
Cardiac output	63	4.37	1.38	4.02-4.71
Cardiac index	65	2.65	0.89	2.43-2.88
Systemic vascular resistance	65	2363.47	949.35	2128.23-2598.71
E/A	77	1.16	0.36	1.08-1.25
E/e'	78	9.77	3.49	8.98-10.56
CVP	76	11.25	5.23	10.05-12.44

LVEF-Left ventricular ejection fraction, E/A- measure of mitral annulus in apical four chamber view of the heart in echocardiography, E/e'- measure of mitral medial annulus in apical chamber view of the heart in echocardiography, CVP-central venous pressure.

Table 12 CARDIOVASCULAR MANIFESTATIONS IN SCRUB TYPHUS

6.9.3 Electrocardiography

Sinus tachycardia was the most common ECG presentation, seen in 38 (46.9%) patients. QRS morphology changes were seen in 11 patients. ST-T changes were seen in 9 patients and 8 patients had T wave inversions. Tachyarrhythmia was seen in 5 patients of whom 3 patients had atrial fibrillation, one patient with supraventricular tachycardia (paroxysmal supraventricular tachycardia) and one patient with wide QRS tachycardia. Bradyarrhythmia was seen in 5 patients, all 5 patients had sinus bradycardia.

ELECTROCARDIOGRAPHIC FINDINGS IN SCRUB TYPHUS	
Sinus Tachycardia	38(46.9)
ST-T changes	10 (12.3)
T wave inversion	8 (9.9)
QRS morphology changes	11 (13.6)
Supraventricular tachycardia	1 (1.2)
Atrial fibrillation	3 (3.7)
Wide QRS tachycardia	1 (1.2)
Sinus bradyarrhythmia	5 (6.2)

Table 13 ELECTROCARDIOGRAPHIC CHANGES IN SCRUB TYPHUS

6.9.4 Pericardial effusion

The presence of pericardial effusion was assessed in all patients in the apical four chamber view and the sub costal view; forty one patients (51%) of them had significant pericardial effusion. However none of them had severe effusion causing right ventricular collapse or requiring pericardiocentesis. The findings are summarized in Figure 26.

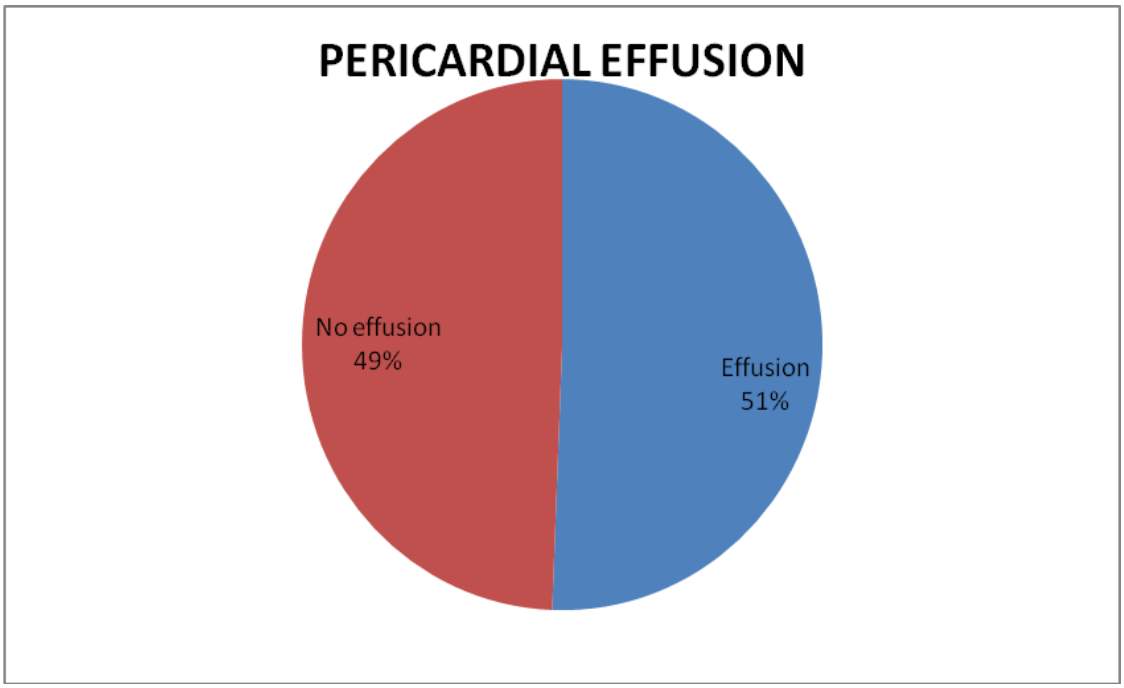


Figure 24 Presence of pericardial effusion in patients with Scrub Typhus

6.9.5 Regional wall motion abnormality

The presence of regional wall motion abnormality (RWMA) was evaluated in all patients in the parasternal short axis and apical four chamber view. Twelve patients had regional wall motion abnormality of which 7 had evidence of myocarditis.

6.10 OUTCOME MEASUSURES

The outcome variables were classified as cardiac and non cardiac variables. The primary outcome was to look at the prevalence of myocarditis.

6.10.1 Primary outcomes

The presence of myocarditis was seen in 17 patients (21%) of the study population. Twenty five of them had myocardial dysfunction as evidenced by left ventricular ejection fraction of less than fifty percent. Fifty patients (61.7%) of them had myocardial injury. Among these patients, 17 had myocarditis and 16 had evidence of renal dysfunction (creatinine more than 1.4mg %). The rest 17 had elevation of troponin T without myocarditis or any obvious confounders causing an elevation. Diastolic dysfunction was measured by mitral inflow pattern (E/A) and mitral annulus velocities (E/e'). Eighteen patients (22%) had evidence of diastolic dysfunction.

6.10.2 Secondary outcomes

Forty nine patients (60.5%) required intensive care admission and 46 (56.8%) were in shock needing vasoactive agents. The various vasoactive agents used were dobutamine (n-16), dopamine (n-25), epinephrine (n-21) and nor epinephrine (n-35). The number of patients requiring ventilation was 48 (59.3%), 39 required invasive ventilation and 15 required only non invasive ventilation. Six patients required both noninvasive and invasive ventilation. Only 4 patients in the cohort required haemodialysis. The mean ± SD duration of ICU and hospital days was 4.2 ± 4.4 and 9.2 ± 4.7 respectively. The overall hospital mortality which included 2 patients discharged at request (one patient from ICU and one patient from general ward) was 9.9%. Of the 8 patients, 7 were managed in the ICU care.

OUTCOME VARIABLES IN PATIENTS WITH SCRUB TYPHUS (n-81)	
Primary outcomes	
Variable	Frequency (%)
Myocarditis	17 (21)
Myocardial dysfunction	25 (30.9)
Myocardial injury	50 (61.7)
Diastolic dysfunction	18 (22.2)
Secondary outcomes	
Needing ICU care	49 (60.5)
Vasoactive agents (shock)	46 (56.8)
Dobutamine	16 (19.7)
Digoxin	14 (17.3
Dopamine	25 (30.9)
Epinephrine	21 (25.9)
Nor epinephrine	35 (43.2)
Needing ventilation	48 (59.3)
Needing hemodialysis	3 (4)
Duration of ICU stay, mean ± SD days	4.2 ± 4.4
Duration of hospital stay, mean ± SD days	9.2 ± 4.7
ICU mortality	7 (8.6)
Hospital mortality	8 (9.9)

ICU- Intensive Care Unit

Table 14 SUMMARY OF OUTCOMES

USE OF DIFFERENT INOTROPES IN SCRUB TYPHUS PATIENTS (n-81)

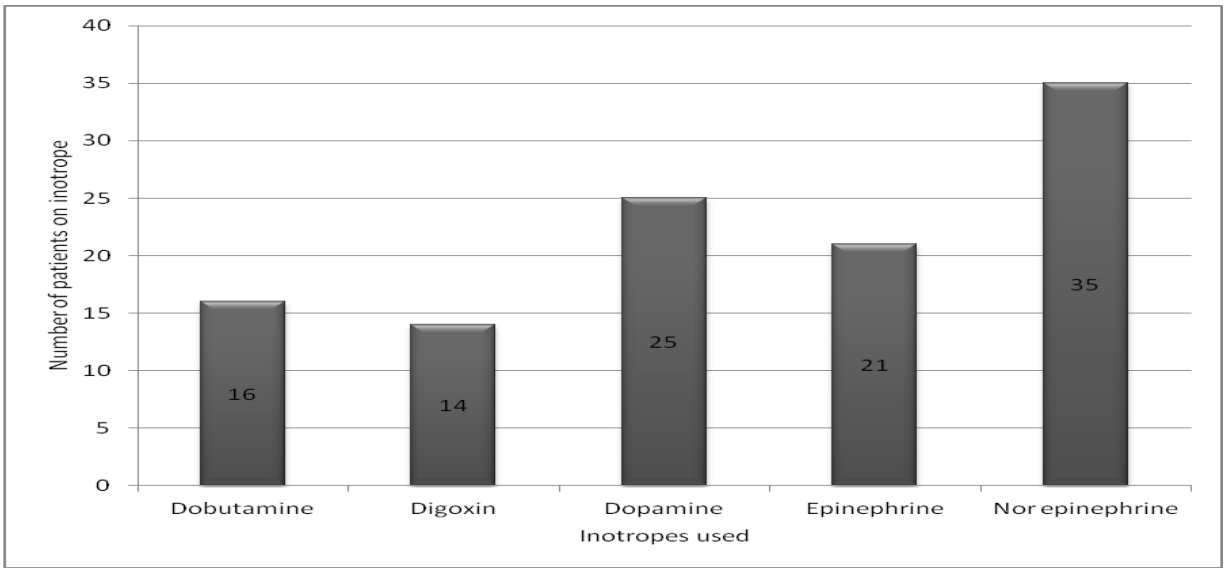


Figure 25 VASOACTIVE AGENTS REQUIREMENT IN SCRUB TYPHUS

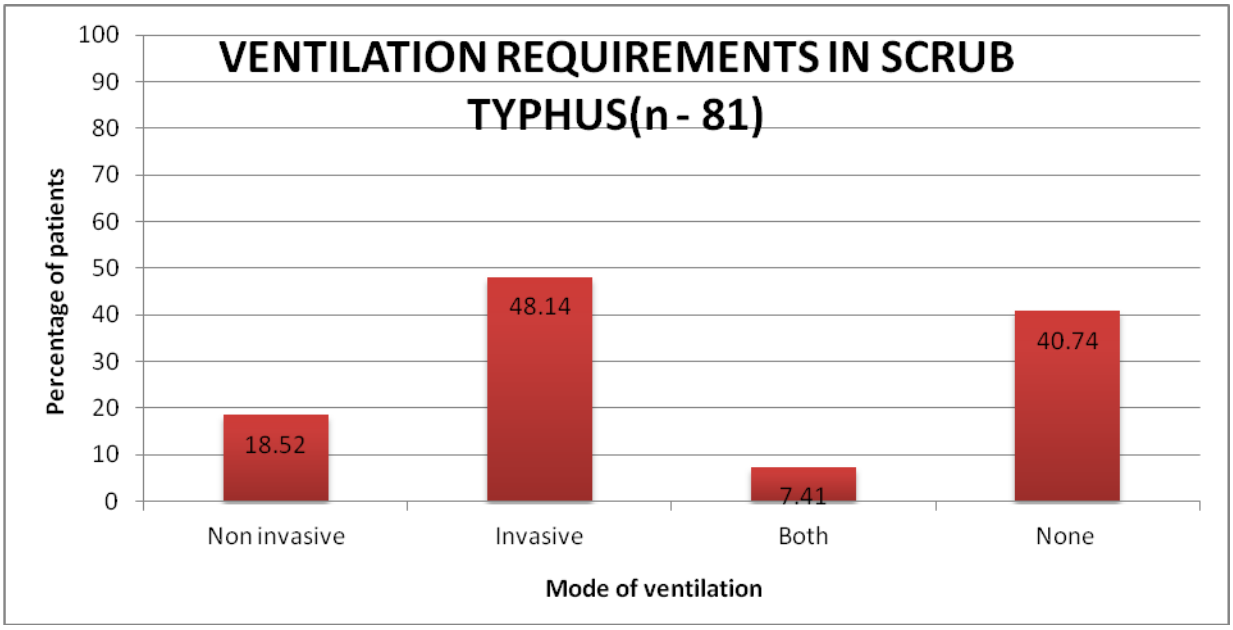


Figure 26 VENTILATORY REQUIREMENTS IN PATIENT WITH SCRUB TYPHUS

6.11 COMPARISON OF SCRUB TYPHUS PATIENTS, WITH AND WITHOUT MYOCARDITIS:

The number of patients with myocarditis, in this cohort was 17 (21%), these patients were compared with the rest of the cohort to look for predictors for myocarditis and the difference among them were studied under the following groups:

6.11.1 Baseline characteristics

The age and gender ratio were similar in both the groups, the duration of illness prior to presenting to the hospital was less in the myocarditis group when compared to patients without myocarditis.

COMPARISON OF BASELINE CHARACTERISTICS: SCRUB TYPHUS WITH MYOCARDITIS AND WITHOUT MYOCARDITIS

Variable	With Myocarditis	Without Myocarditis	P value
Age (mean ± SD)years	48.76 ±16.32	49.56 ± 16.13	0.85
Gender ratio (male/female)	7:1	28:36	1.00
Duration of illness, (mean ±SD) days	6.88 ± 2.82	8.44 ± 3.12	0.067
From TN number (%)	9 (52.9)	44 (68.8)	0.258
From AP number (%)	8 (47.1)	20 (31.2)	0.258

LVEF- left ventricular ejection fraction, TN-Tamil Nadu, AP-Andhra Pradesh

Myocarditis (patients with left ventricular ejection fraction less than 50 % and troponin T more than 14pg/ml)

Table 15 COMPARISON OF BASELINE CHARACTERISTICS IN SCRUB TYPHUS PATIENTS WITH AND WITOUT MYOCARDITIS

6.11.2 Comparison of symptomatology

All patients in this cohort had fever as the presenting compliant. Breathlessness was more commonly seen in patients with myocarditis group (82. 4%) as compared to patients without myocarditis (59.4%); however it was not statistically different. More patients without myocarditis presented with cough (n-24) 37.5% when compared with those who did not develop myocarditis (n-5) 29.4%. Vomiting and myalgia were more commonly seen in patents with myocarditis.

COMPARISON OF SYMPTOMATOLOGY: SCRUB TYPHUS WITH AND WITHOUT MYOCARDITIS (n-81)

Symptom	With Myocarditis Number (%)	Without Myocarditis Number (%)	P value
Fever	17 (100)	64 (100)	-
Cough	5 (29.4)	24 (37.5)	0.584
Breathlessness	14 (82.4)	38 (59.4)	0.389
Altered mental status	3 (17.6)	12 (18.8)	1.00
Myalgia	7 (41.2)	15 (23.4)	0.449
Vomiting	7 (41.2)	15(23.4)	0.218

Myocarditis (patients with left ventricular ejection fraction less than 50 % and troponin T more than 14pg/ml

Table 16 COMPARISON OF SYMPTOMATOLOGY IN SCRUB TYPHUS PATIENTS WITH AND WITHOUT MYOCARDITIS

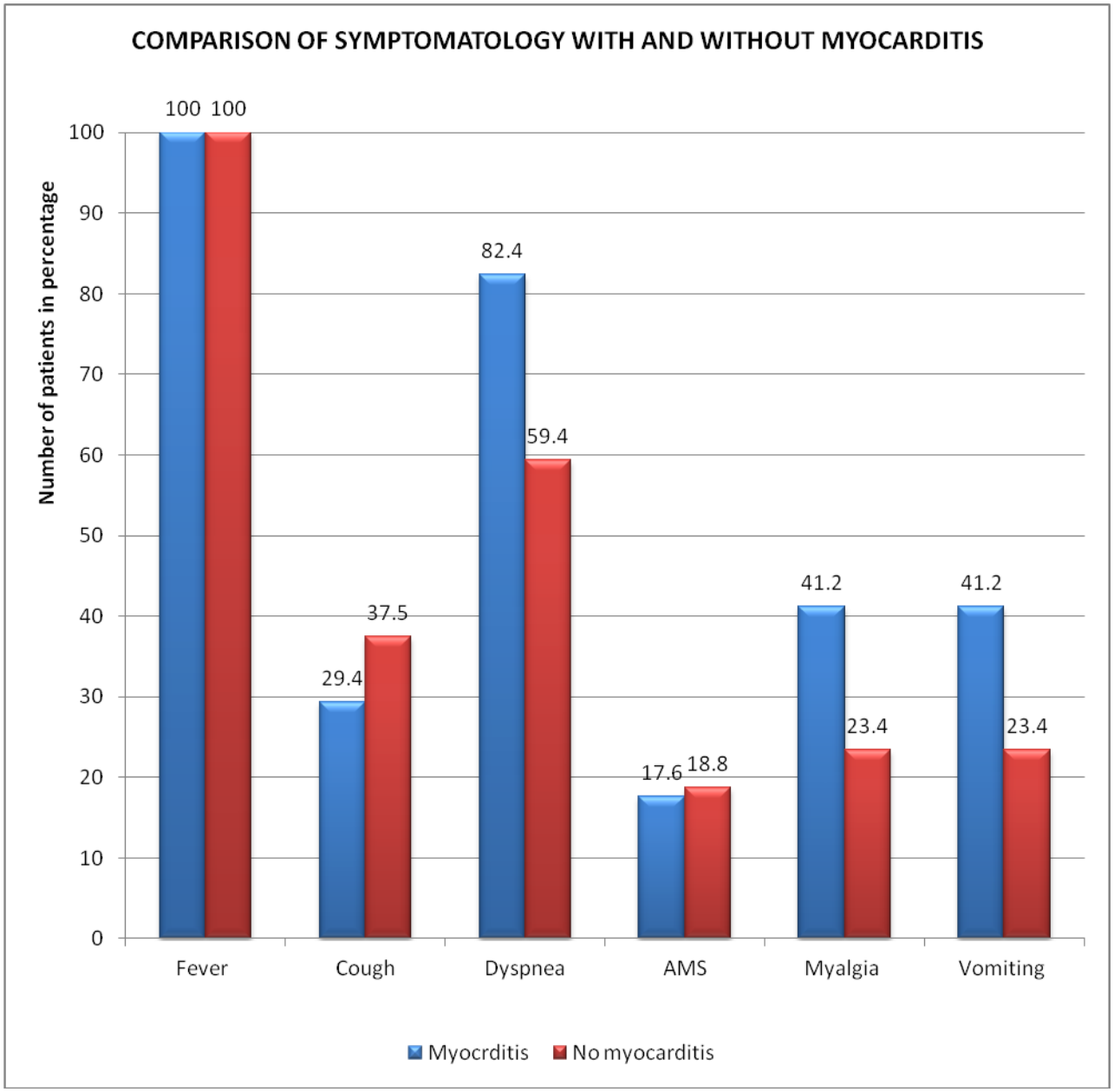


Figure 27 COMPARISON OF SYMPTOMATOLOGY IN PATIENTS WITH AND WITHOUT MYOCARDITIS.

6.11.3 Comparison of laboratory parameters

The myocarditis group had a mild elevation in hemoglobin and a slight decrease in total counts. The degree of thrombocytopenia was more prominent in the myocarditis group with a mean platelet counts of 52900 cmm as compared to 74100 cmm in the group without myocarditis. There was a mild decrease in creatinine and albumin levels in the myocarditis group.

COMPARISON OF LABORATORY PARAMETERS OF SCRUB TYPHUS WITH AND WITHOUT MYOCARDITIS			
VARIABLE	WITH MYOCARDITIS	WITHOUT MYOCARDITIS	P VALUE
Creatinine, mean ± SD, mg %	1.55 ± 0.89	1.77 ± 1.55	0.580
Hemoglobin, gm %	12.04 ± 3.69	11.24 ± 2.17	0.259
Total counts, cmm	8570.59 ± 3803.24	10900 ± 4969.67	0.072
Platelets , cmm	52900 ± 25969.86	74100 ± 77598.25	0.272
Total bilirubin, mg %	1.62 ± 1.38	2.14 ± 2.04	0.296
Direct bilirubin, mg %	1.23 ± 1.350	1.64 ± 1.79	0.384
Serum albumin, gm %	2.359 ± 0.799	2.641 ± 0.505	0.077
SGOT U/L	149.88 ± 84.22	136.17 ± 94.87	0.590
SGPT U/L	66.76 ± 43.87	69.16 ± 50.98	0.860
Alkaline phosphatase, U/L	194.59 ± 123.17	200.34 ± 103.35	0.845
SGOT-Serum Glutamic –Oxaloacetic transaminase, SGPT- Serum Glutmic Pyruvic Transaminase**.**			

Table 17 COMPARISON OF LABORATORY PARAMETERS IN PATIENTS WITH AND WITHOUT MYOCARDITIS

The creatinine and albumin means were 1.55mg % and 2.36 gm % in the myocarditis group, while in the group without myocarditis the mean creatinine and albumin were 1.77 mg % and 2.64 gm % respectively.

6.11.4 Comparison of scoring system and organ dysfunction

The various organ dysfunctions were assessed using SOFA score, and APCAHE II score was used to predict the mortality. Patients with myocarditis had a higher SOFA and APACHE II score; however only SOFA score was statistically significant, the mean ± SD SOFA score in patients with myocarditis and without myocarditis were 10.82 ± 3.02 and 8.43 ± 4.03 respectively. The predicted mortality in the myocarditis group was 30.24 %, in the group without myocarditis it was 25.19%.

COMPARISON OF SCORING SYSTEM AND ORGAN DYSFUNCTION AMONG SCRUB TYPHUS WITH AND WITHOUT MYOCARDITIS

Variable	With Myocarditis (n-17) Mean ± SD	Without Myocarditis (n-64) Mean ± SD	P value
SOFA score	10.82 ± 3.02	8.43 ± 4.03	0.026
APACHE II	17.35 ± 7.49	15.12 ± 6.95	0.254
Predicted mortality	30.24 ± 21.06	25.19 ± 17.91	0.323

Table 18 COMPARISON OF SCORING SYSTEM OF ORGAN DYSFUNCTION IN PATIENTS WITH AND WITHOUT MYOCARDITIS

Comparison of SOFA scores:

On the basis of SOFA score the organ involvement was classified into organ dysfunction and organ failure, the predominant organ dysfunction seen in the myocarditis group was renal (n-9) 52.9%, in patients without myocarditis renal involvement was seen in (n-27) 42.2%. Cardiovascular dysfunction was seen almost equally in both the groups, 11.8 % (n-2) and 10.9% (n-7). On comparing organ failure, cardiovascular organ failure was more commonly seen in patients with myocarditis as compared to those without myocarditis, 82.3% (n-14) and 43.7% (n-28) respectively and this was significantly different.

COMPARISON OF ORGAN DYSFUNCTION USING SOFA SCORE: SCRUB TYPHUS WITH AND WITHOUT MYOCARDITIS

Organ	With Myocarditis (n-17) n (%)	Without Myocarditis (n- 64) n (%)	P value
Respiratory	8 (47.1)	36 (56.2)	0.588
Cardiovascular	2 (11.8)	7 (10.9)	1.00
liver	8 (47.1)	28 (43.7)	1.00
Hematological	6 (35.3)	29 (45.3)	0.585
Central nervous system	2 (11.8)	7 (10.9)	1.00
Renal	9 (52.9)	27 (42.2)	0.584

SOFA- Sequential Organ Failure Assessment

Table 19 COMPAISON OF ORGAN DYSFUNCTION IN PATIENTS WITH AND WITHOUT MYOCARDITIS

COMPARISON OF ORGAN FAILURE USING SOFA SCORE: SCRUB TYPHUS WITH AND WITHOUT MYOCARDITIS			
Organ	With Myocarditis n (%)	Without Myocarditis n (%)	P value
Respiratory	9 (52.9)	20 (31.2)	0.153
Cardiovascular	14 (82.3)	28 (43.7)	0.006
liver	1 (5.8)	7 (10.9)	1.00
Hematological	11 (64.7)	32 (50)	0.413
Central nervous system	1 (5.8)	5 (7.8)	1.00
Renal	1 (5.8)	6 (9.4)	1.00
In Myocarditis group n- 17 and non Myocarditis group n-64			

Table 20 COMPARISON OF ORGAN FAILURE IN PATIENTS WITH AND WITHOUT MYOCARDITIS

6.11.5 Comparison of secondary outcomes

The secondary outcomes were compared between scrub typhus patients with myocarditis (n-17) and without myocarditis (n-64). More patients with myocarditis (82.3%) were admitted to the ICU when compared with those without myocarditis (54.7%), which was significantly different. Scrub typhus patients with shock (requiring vasoactive agents) were more predominant in the myocarditis group, (94.1%) as compared to patients without myocarditis (46.9%), and this was significantly different. Fourteen patients (82.3%) in the myocarditis group required ventilator support, where as 30 patients (46.9%) without Myocarditis required ventilation which was significantly different. The myocarditis group tended to stay longer in hospital, 11.7 ±4.63 (mean ± SD) days as compared to group without myocarditis 8.59 ± 4.52 (mean ± SD) days, which was statistically significant.

COMPARISON OF OUTCOME IN SCRUB TYPHUS WITH AND WITHOUT MYOCARDITIS			
Variable	With myocarditis	Without myocarditis	P value
Needing ICU care, n (%)	14 (82.3)	35 (54.7)	0.051
Inotropic support (shock) n (%)	16 (94.1)	30 (46.9)	0.00
Needing ventilation n (%)	14 (82.3)	34 (53.1)	0.05
Needing haemodialysis n (%)	1 (5.8)	3 (4.7)	1.00
Duration of ICU stay, mean ± SD days	3.66 ± 4.37	6.06 ± 4.37	0.0474
Duration of hospital stay, mean ± SD days	11.7 ± 4.63	8.59 ± 4.52	0.014
ICU mortality n (%)	1 (5.9)	6 (9.3)	1.00
Hospital mortality n (%)	1 (5.9)	7 (10.9)	1.00
ICU- Intensive Care Unit, with Myocarditis- (n-17), without Myocarditis- (n-64)			

Table 21 COMPARISON OF OUTCOMES IN PATIENTS WITH SCRUB TYPHUS WITH AND WITHOUT MYOCARDITIS

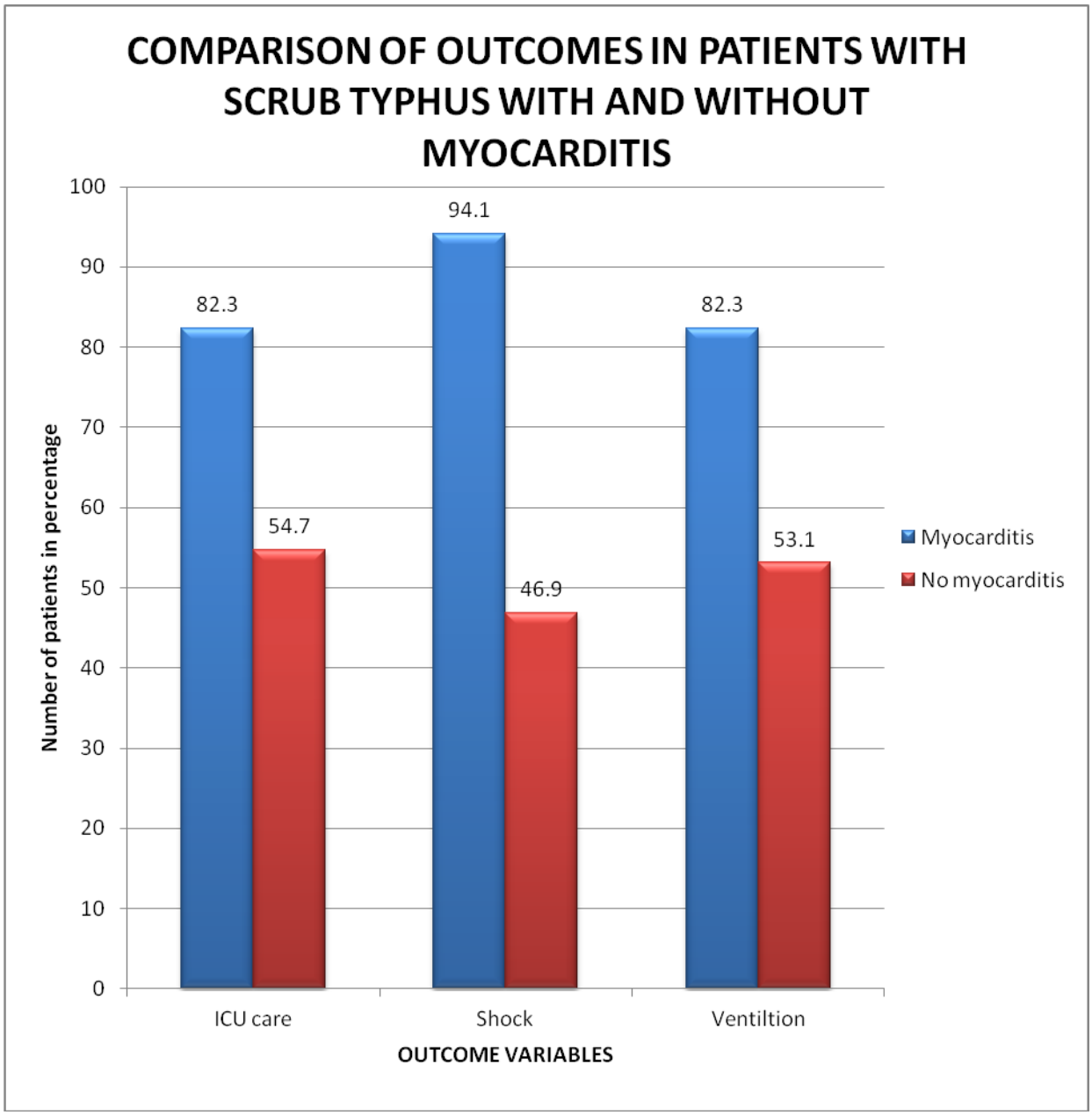


Figure 28 COMPARISON OF OUTCOMES IN PATIENTS WITH SCRUB TYPHUS

ICU- intensive Care Unit, shock- patients requiring vasoactive, myocarditis group (n-17), no myocarditis group (n-64)

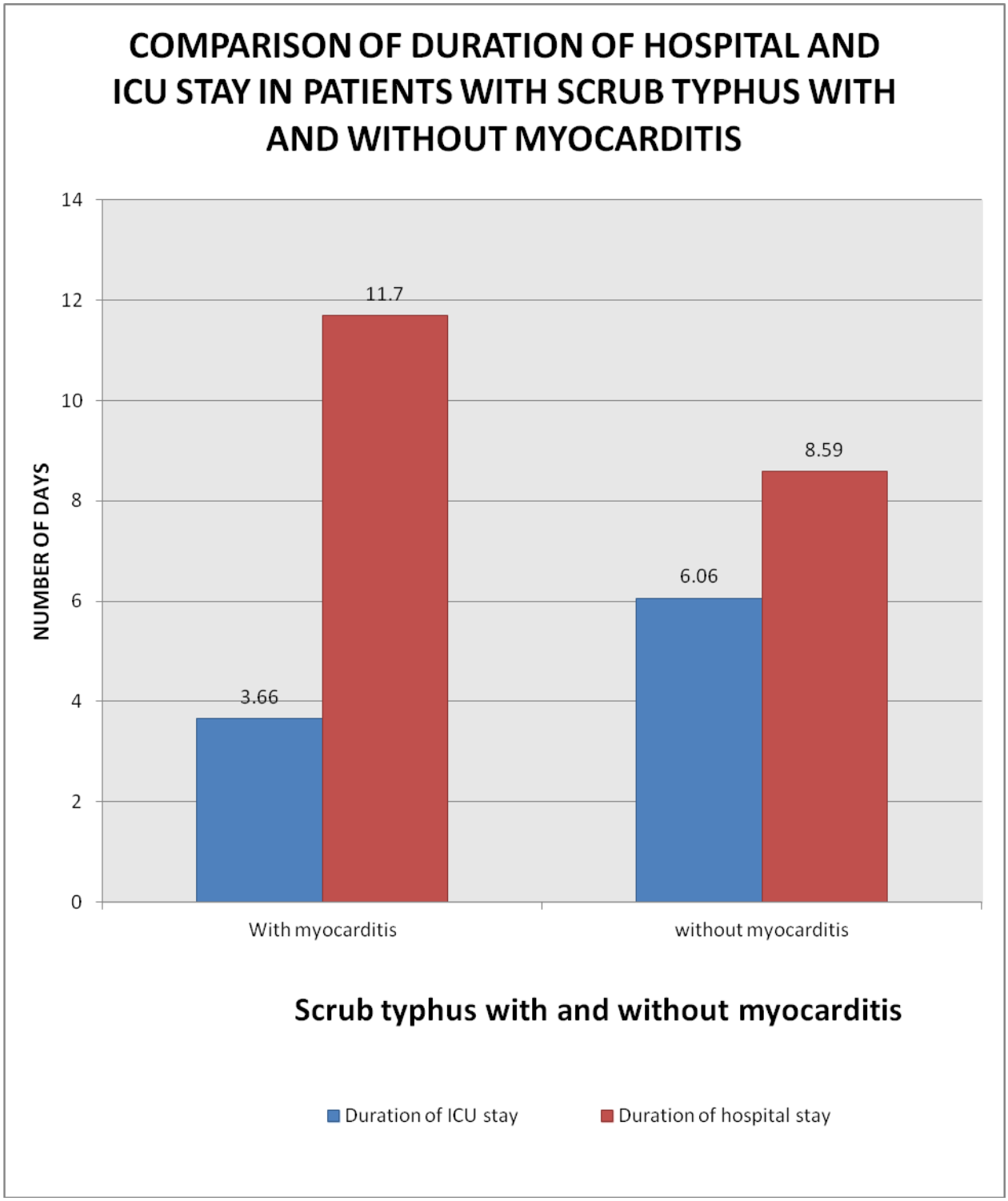


Figure 29 COMPARISON OF DURATION OF HOSPITAL AND ICU STAY IN PATIENTS WITH SCRUB TYPHUS WITH AND WITHOUT MYOCARDITIS

6.11.6 Comparison of the different types of shock and use of vasoactive agents

In this cohort of patients, the presence of shock was defined as individuals with systolic blood pressure less than 90 and requiring vasoactive agents. The use of vasoactive agents were more in the myocarditis group as compared to the group without myocarditis. Dobutamine was used in 8 patients (47.1%) with myocarditis and 8 patients (12.5%) in the group without myocarditis. The most commonly used vasoactive agent was nor epinephrine, used in 12 (70.6%) patients with myocarditis and in 25 (39.1%) patients without myocarditis. Eight (47.1%) patients in the myocarditis group received digoxin, of which 7 patients were on dobutmine as well. In patients without myocarditis digoxin was used in 6 (9.4%) patients. Dopamine and epinephrine were used in 6 (35.3%) patients in the myocarditis group and in patients without myocarditis, dopamine was used in 19 (29.7%) and epinephrine was used in 15 (23.4%) patients.

COMPARISON OF THE USE OF VASOACTIVE AGENT IN SCRUB TYPHUS PATIENTS WITH AND WITHOUT MYOCARDITIS

Variable	With myocarditis Number (%)	Without myocarditis Number (%)	P value
Dobutamine	8 (47.1)	8 (12.5)	0.04
Digoxin	8 (47.1)	6 (9.4)	0.01
Dopamine	6 (35.3)	19 (29.7)	0.796
Epinephrine	6 (35.3)	15 (23.4)	0.358
Nor epinephrine	12 (70.6)	25 (39.1)	0.028

Table 22 COMPARISON OF VASOACTIVE AGENTS IN SCRUB TYPHUS PAIENTS WITH AND WITHOUT MYOCARDITIS

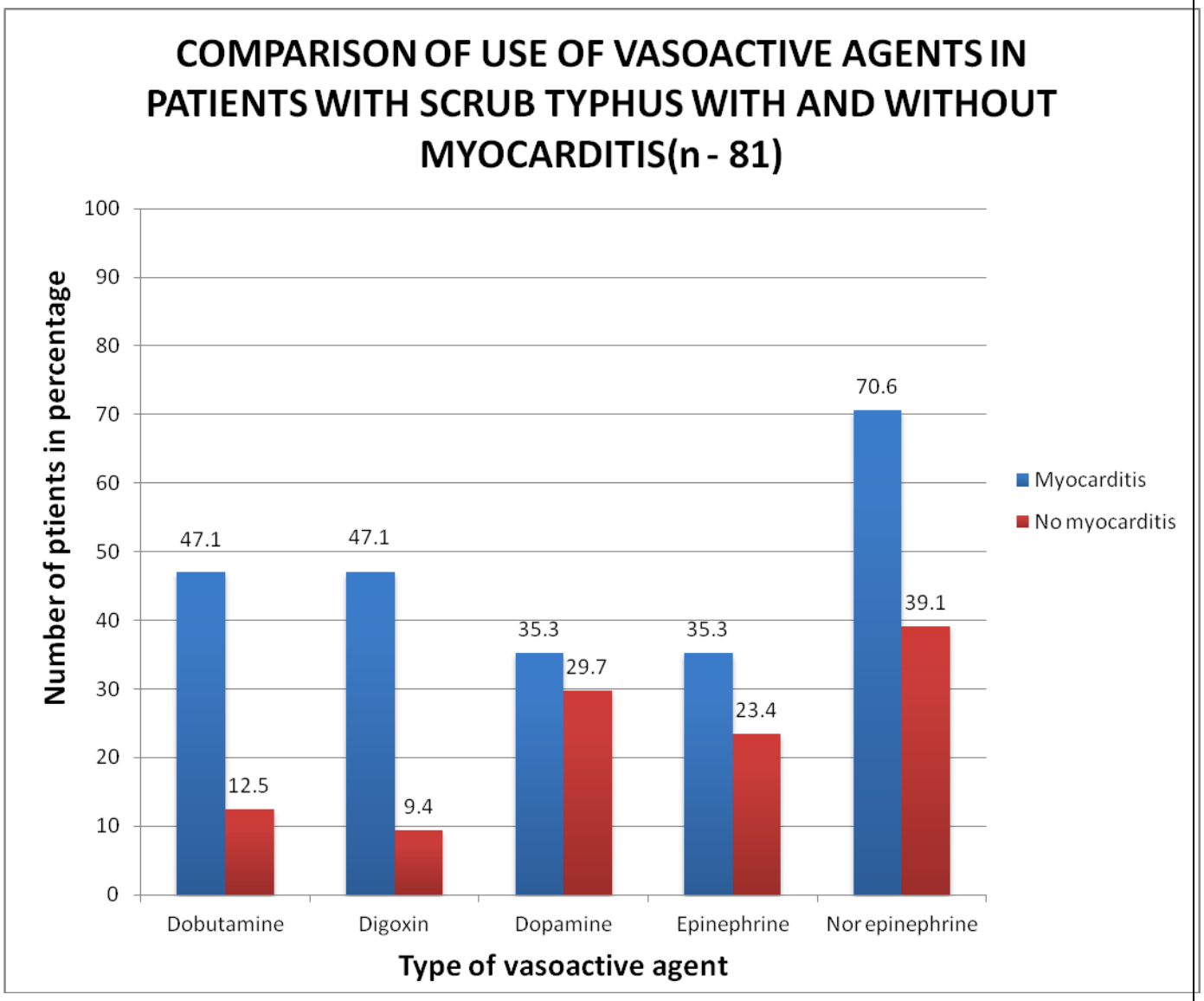


Figure 30 COMPARISON OF VASOACTIVE AGENTS IN PATIENTS WITH SCRUB TYPHUS WITH AND WITHOUT MYOCARDITIS

6.11.7 Types of shock

The type of shock was classified on the basis of echocardiograhy parameters, where variables such as cardiac index (CI), systemic vascular resistance index (SVRI) and central venous pressure (CVP) were used to classify shock as cardiogenic, septic, hypovolemic or mixed. A total of 67 patients (including patients not requiringvasoactive agent) were assessed for nature of shock, in the myocarditis group 17 patients (16 patients were requiring vasoactive agent) and the rest 50 patients were without myocarditis. In myocarditis group 9 patients had features of cardiogenic shock, 4 patients had features of septic shock and 4 had features of mixed shock. In patients without myocarditis cardiogenic nature of shock was seen in 22 patients, 6 patients had features of sepsis. Hypovolemic and mixed type of shock were seen in 9 and 13 patients respectively.

COMPARISON OF DIFFERENT TYPES OF SHOCK IN SCRUB TYPHUS PATIENTS WITH AND WITHOUT MYOCARDITIS

Type of shock	Myocarditis	Without myoacrditis
Cardiogenic	9	22
Septic	4	6
Mixed	4	13
Hypovolemic	0	9

Table 23 COMPARISON OF TYPES OF SHOCK IN SCRUB TYPHUS PATIENTS WITH AND WITHOUT MYOCARDITIS

6.12 Systemic Vascular Resistance Index vs. Cardiac Index

The scatter plot below shows sytemic vascular resistance index (SVRI) vs. cardiac index (CI), towards the right end of the plot are patients with high SVRI and a low CI, implies cardiogenic shock.

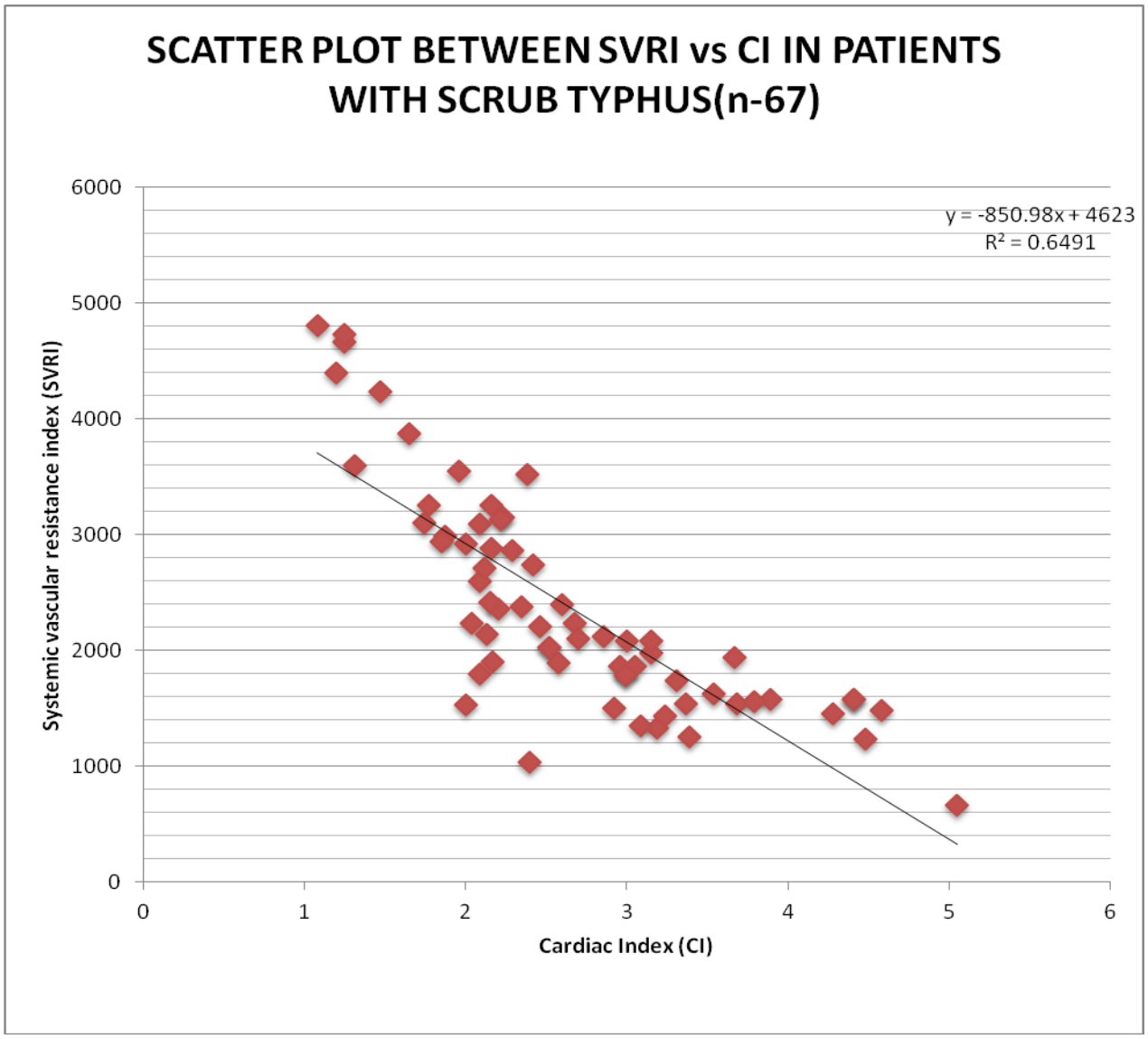


Figure 31 – SYSTEMIC VASCULAR RESISTANCE AGAINST CARDIAC INDEX IN PATIENTS WITH SCRUB TYPHUS

Cardiac Index normal range- 2.6–4.2 L/min/m^2 , Systemic vascular resistance index -normal range- 1700-2400 of dyn·s·cm^{-5}

Low CI with high SVRI- suggestive of cardiogenic shock

High CI with low SVRI – suggestive of septic shock

Towards the left and bottom of the plot are representing patients with high CI and a low SVRI suggesting septic shock.

The patients ploted in the centre of the plot are the once with mixed shock.

In scrub typhus there is a distribution of shock from the high cardiac index low SVRI septic shock to the low cardiac index high SVRI cardiogenic shock.

The cardiogenic shock seems to be predominant shock, seen in nearly fifty percent of the patients assessed. This is summarised in the Figure 33

6.13 PREDICTORS OF MYOCARDITIS

6.13.1 Baseline characteristics

Bivariate logistic regression analysis was done to predict factors associated with the development of myocarditis in scrub typhus, among the various parameters, age, sex and duration of illness were the baseline characters used, of which duration of illness was found significant. The presence of eschar and pericardial effusion were not found to be significant in predicting myocarditis.

BIVARIATE LOGISTIC REGRESSION OF PREDICTORS OF MYOCARDITIS IN SCRUB TYPHUS (n- 81)- USING BASELINE CHARCTERISTICS

Variable	Odds ratio	P value	95% CI
Age	0.997	0.852	0.964 – 1.031
Sex	1.111	0.849	0.375 – 3.288
Fever	0.831	0.072	0.679 – 1.017
Eschar	1.556	0.527	0.395 – 6.117
Effusion	1.521	0.448	0.515 – 4.492
Creatinine	0.882	0.579	0.566 – 1.375
SOFA score	1.171	0.031	1.014 – 1.351
APACHE II	1.044	0.253	0.969 – 1.126

SOFA- Sequential Organ Failure Assessment, APACHE- Acute Physiology and Chronic Health Evaluation, ICU- Intensive Care Unit, CI- Confident Interval

Table 24 BIVARIATE LOGISTIC REGRESSION OF PREDICTORS OF MYOCARDITIS IN SCRUB TYPHUS

Among the scoring system used, SOFA and APACHE II, patients developing myocarditis tended to have a higher SOFA score, but not APACHE II score. Comparing creatinine values in the myocarditis and without myocarditis did not help in predicting myocarditis.

6.13.2 Outcome variables

On performing bivariate logistic regression analysis of predictors of myocarditis using the outcome variables, the need for dialysis and hospital outcome was not predictive of myocarditis. The presence of myocarditis was associated with an increased need for mechanical ventilation ($p<0.035$) and prolonged ICU ($p<0.055$) and hospital stay ($p<0.020$).

UNIVARIATE LOGISTIC REGRESSION OF PREDICTORS OF MYOCARDITIS IN SCRUB TYPHUS (n- 81)- USING OUTCOME VRIABLES

Variable	Odds ratio	P value	95% CI
Dialysis	1.875	0.617	0.159 – 22.01
Ventilation	4.242	0.035	1.109 – 16.22
ICU duration	1.212	0.055	0.998 – 1.261
Hospital duration	1.142	0.020	1.021 – 1.278
Hospital outcome	0.509	0.541	0.058 – 4.446

Table 25 UNIVARIATE LOGISTIC REGRESSION OF PREDICTORS OF MYOCARDITIS IN SCRUB TYPHUS USING OUTCOMES

6.13.3 Multivariate Analysis

A multivariate logistic regression analysis was done using factors identified on bivariate analysis to be associated with myocarditis. After adjusting for severity of illness and ventilator need, only duration of illness was associated with myocarditis.

MULTIVARIATE ANALYSIS OF PREDICTORS OF MYOCARDITIS

Variable	0dds ratio	P value	95% C I
Duration of illness	0.7157	0.020	0.5404 – 0.9478
SOFA	1.1348	0.267	0.9078 – 1.418
Duration of hospital stay	1.152	0.059	0.9947 – 1.3345
Ventilation	1.405	0.709	0.2355 – 8.3851

SOFA- Sequential Organ Failure Assessment, CI- confidence interval.

Table 26 MULTIVARIATE ANALYSIS OF PREDICTORS OF MYOCARDITIS

6.13.4 The Receiver Operator Curve (ROC) to look for predictors of Myocarditis

ROC curve was used to look for predictors of myocarditis. The variables used were SOFA score and APACHE II score.

SOFA score has been shown to predict mortality in critically ill patients. We used SOFA score in this cohort of patients to look for prediction of myocarditis.

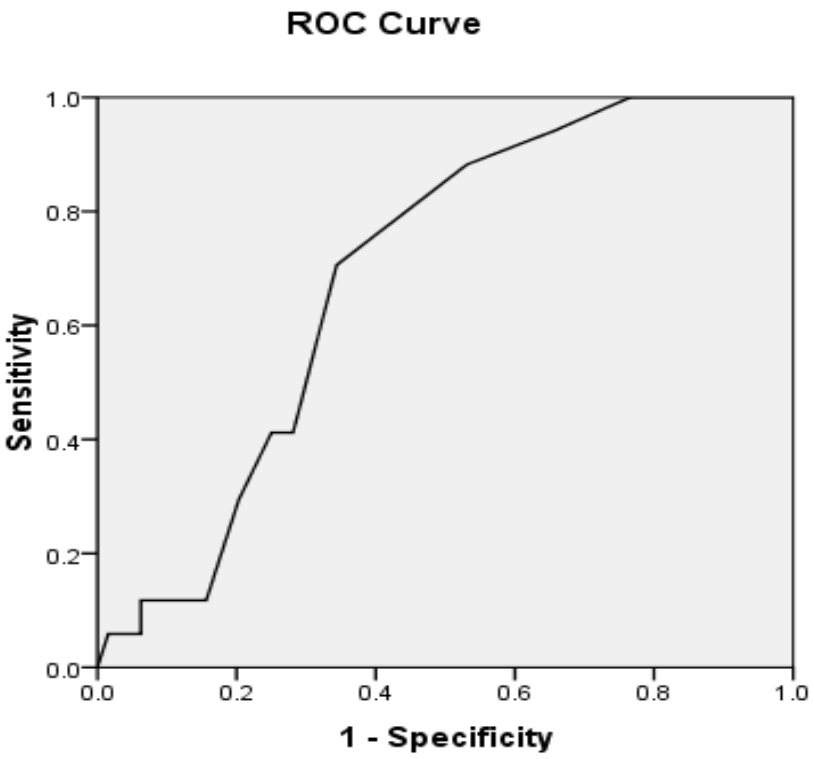


Figure 32 ROC CURVE – PREDICTORS OF MORTALITY (SOFA)

On plotting , the area under the curve was 0.546 which was not significant.

6.13.5 The Receiver Operator Curve (ROC) for APACHE II score and Myocarditis

APACHE II score is used in predicting mortality, in this cohort of patients the role of APACHE II in predicting myocarditis was analyzed with the help of ROC curve. All 81 patients APACHE II score was calculated and included for analysis.

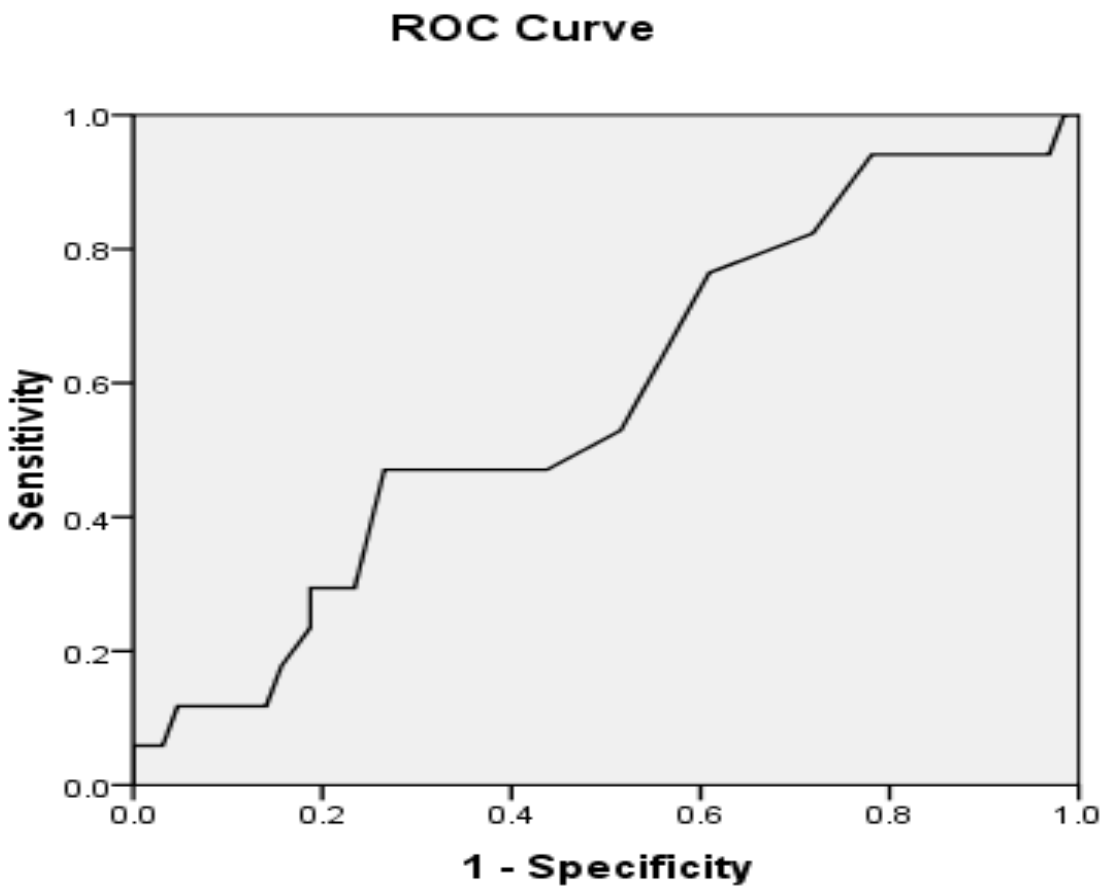


Figure 33 ROC CURVE – PREDICTORS OF MYOCARDITIS (APACHE II)

On plotting the area under the curve was 0.579, which was not significant.

7. DISCUSSION

Scrub typhus is one of the common causes of acute febrile illness with multiorgan dysfunction. It is known that myocarditis can occur in association with scrub typhus infection. However the magnitude and impact of cardiac manifestations in scrub typhus are unknown. In one of the earliest pathologic studies, Levine et al (24) described 31 patients with scrub typhus with cardiovascular involvement. There have been case reports and small case series of myocarditis in scrub typhus (27,41). This prospective cohort study describes scrub typhus patients and their various cardiac manifestations. The sample size of 84 was calculated assuming a prevalence of myocarditis of 30% myocarditis. One hundred and twenty-two patients were screened for myocarditis of whom 19 patients had other etiology like dengue, malaria, enteric fever, leptospirosis and spotted fever. Eighty-one patients with confirmed scrub typhus infection were included in the analysis; myocardial injury was observed in 50 (61.7%) patients whereas myocardial dysfunction was seen in 25 (30.9%) patients. A diagnosis of myocarditis was presumed in 17 (21%) of patients in whom myocardial dysfunction and myocardial injury were evident.

In our cohort of patients the mean age was 49.41 ± 16.07 years, the duration of illness prior to presentation was 8.11 ± 3.11 days and patients were predominantly from Tamil Nadu and its neighboring state Andhra Pradesh. These findings were similar to the previous studies on scrub typhus by Chrispal et al (1) and Griffith et al (2). A female predominance was seen in our cohort of patients, similar to other studies by Varghese et al (23) and Kim et al (10).

The most common presenting symptom in our study was fever (100%), followed by breathlessness (75.5%); the other symptoms commonly seen were myalgia, cough, vomiting and altered sensorium. Varghese et at (23), in their cohort of 625 patients had reported fever in all patients and breathlessness in 49%. Chrispal et at (1) had shown the presenece of fever in all patients with breathlessness in 37.6% of the 198 patients studied in their cohort. The presence of fever in all patients was common in our study as compared to the rest, and more number of patients in our study group had presented with breathlessness. This is probably due to selection bias where a relatively more number of sicker patients were included in our cohort (60.5% patients required ICU care).

Diabetes mellitus was the most common cormorbid illness seen in 16 (19.7%) patients followed by hypertension in 15 (18.5%). The presence of diabetes and hypertension in study by Varghese et at (23) was 11.4% and 12% respectively. A slight increase in the proportion of cormorbid illness in our study group could have been contributed to the small sample size. There was no patient in the study group with history of chronic immunosupression or features of autoimmune disease which can contribute to myocarditis. The number of patients with history of smoking and alcohol consumption was less in our cohort, this could be due to presence of female predominance and information bias.

The presnece of eschar on meticulous examination was seen in 62 (77%) patients and other stuies had shown an eschar detection rate between 46-86% (21). The high detection rate of eschar reflects the knowledge acquired by physicians.

The common laboratory findings included thrombocytopenia (92.6%), elevated transaminases (92.6%), leukocytosis (51.8%) and a rise in creatinine. The transaminitis was mild, with SGOT being more than the SGPT suggesting a mitochondrial injury rather than a hepatic injury. In our study a low albumin (less than 2.5 gm %) was seen in 39 (48.1%) patients. Kim et al (42) reported the presence of a low albumin (less than 3.0 gm %) in 16.3% of their study group and hypoalbuminemia was associated with significant mortality. The pathogenic mechanism of hypoalbuniemia in scrub typhus is not established. However it has been postulated that due to vasculitis, secondary to scrub typhus, there is an increase in vascular permeability causing plasma protien leakage.

The various organ involvement in the study participants was assessed using SOFA score and APACHE II score. The mean SOFA and APCAHE II score were 8.84 ± 3.95 and 15.68 ± 7.01; the predicted mortality was 25.25 ± 18.59 %. In Griffith et al(2) study on critically ill patients the mean SOFA and APACHE II score were 10.5 and 19.6, and the predicted mortality was 36.3%. this suggests our cohort contianed both critically ill and not so sick patients.

In this cohort of patients, hematological organ dysfunction predominated (96.3%), followed by respiratory system seen in 90.1% and cardivascular involvement in 62.9%. Hepatic and renal involvement were seen in 54.3% and 51.3% respectively. Central nervous system involvement was seen in only 18.5% of patients. These findings are similar to the previous study by Griffith et al (2) where respiratory sytem predominated with 96.6%, followed by hematological 86.2%, hepatic and renal 63.8%, cardiovascular 61.7% and central nervous system 24.3%. The similarity in organ dysfunction between these two different cohort of patients, where Griffith et al(2) looks at a pure ICU cohort and our study, a mixed cohort of ICU and non ICU patients suggest that scrub typhus more commonly affects the respiratory, hematological and

cardivascular system as compared to the rest. The predominant hematological organ involvement in our cohort could be secondary to the selection bias where all patients with acute febrile illness and platelets counts less than 1.5 lakhs were screened for myocarditis.

The median organ involvement in our cohort of patients was 4, and 97.5% of patients had 2 or more organ involvement. This is consistent with the previous studies on scrub typhus which has established scrub typhus as a systemic infection involving multiple organs.

The cardiovascular manifestations were assessed with the help of cardiac biomarkers, electrocardiogram and echocardiogram. The mean (SD) CKMB and troponin T values were 6.69 ± 9.4 ng/ml and 83.1 ± 212.2 pg/ml. As troponin T is a more sensitive marker of myocyte injury in patients with clinically suspected myocarditis (31), it was used in screening patients for myocarditis. However troponin levels can be elevated in several conditions other than myocardial injury particularly in critically ill patients (43). Thus the myocardial injury may have been overestimated in our cohort. However, myocarditis was presumed only if myocardial injury coexisted with global myocardial dysfunction, hence the prevalence of myocarditis in our cohort was not affected by an overestimated myocardial injury rate. Fifty patients had troponin levels more than 14 pg/ml, 17 patients were diagnosed with myocarditis and the other 16 patients had evidence of renal failure. Seventeen patients had an elevated troponin T levels without myocarditis or renal failure suggesting myocardial injury in this subset of patients.

Echocardiography was done in all patients; the mean ± SD left ventricular ejection fraction was 57.59 ± 14.16%. The mean cardiac output was 4.37 ± 1.38liters, and the mean cardiac index (CI) and systemic vascular resistance index (SVRI) were2.65 ± 0.89 and 2363.47 ± 949.35 respectively. A low CI was seen in 33 patients and a high CI in 6 patients. A low SVRI

was seen in 18 patients and a high SVRI in 24 patients. The different types of shock in this cohort of scrub typhus patients were vasoplegic, mixed, hypovolemic and cardiogenic. Cardiogenic type of shock was the most common type of shock; it was seen in 52.9% of patients with myocarditis and 34.3% in those without myocarditis. Twenty five patients had left ventricular systolic dysfunction. We noticed that 18 patients had mild diastolic dysfunction (E/A less than 1). Diastolic dysfunction presenting in scrub typhus has not been described in literature so far, however diastolic dysfunction has been described in other forms of myocarditis, post viral and lymphocytic myocarditis. In our cohort the mean E/A was 1.16 and only 2 patients had E/e' more than 15. We found that all patients with diastolic dysfunction belong to the milder form of the disease, James et al (44) in lymphocytic myocarditis had shown a restrictive pattern of diastolic dysfunction with mean E/A of 2.13 ± 1.3.

In this cohort, 38 patients (46.9%) had sinus tachycardia which was the most common finding. Three patients had atrial fibrillation with no other risk factors for the same. QRS morphology changes were seen in 11 patients. Only 5 patients had bardyarrhythmia and 8 patients had T inversion. One patient had supraventricular tachycardia and one patient had wide QRS tachycardia. None of the patients had heart block. The ECG finding in our cohort of patients were similar to Watt et al (45) where majority of the findings were minor and non-specific .

Pericardial effusion in scrub typhus has been reported as case reports (46,47); Lee et al (48) had described 5 cases of pericardial effusion. There are no large prospective studies in literature looking at the presence of pericardial effusion in scrub typhus, although a high rate of effusion was reported in autopsy studies. In our cohort we found pericardial effusion in 41 patients (51%).

Regional wall motion abnormality was seen in 12 patients, 7 patients had myocarditis. Of the remaining 5 patients, 2 had risk factors of diabetes and hypertension. Two patients were elderly 70 and 83 years old. One patient had documented mitral valve prolapse.

Forty nine patients (60.5%) required ICU care; this suggests that our cohort contained more number of critically ill patients. The patients presenting in shock were 46 (56.8%) in our cohort where as in Varghese et at (23) it was 23.1% and Chrispal et at (1) it was 13.8%. This finding of a relatively high percentage of patients with shock in our cohort was probably due to a selection bias where more number of sick patients was included.

In our cohort, patients with respiratory failure were managed with both invasive and non invasive ventilatory support, 38.50 % of the patients had acute respiratory distress syndrome (ARDS). 48.14% required invasive ventilation and 18.4% required non-invasive ventilation and 7.41% required both forms of ventilation. The mean ± SD duration of ICU and hospital days was 4.2 ± 4.4 and 9.2 ± 4.7 respectively. In Griffith et al(2) study 81% of the patients required ventilation. The patients requiring invasive and non invasive ventilation were 63.8% and 17.2% respectively. The mean duration of ICU and hospital stay in their cohort was 6.3 and 10.7 days. In our cohort the need for ventilation and the duration of ICU and hospital stay were less as compared to Griffith et al(2).

The crude mortality in our cohort was 9.9%, which comparable to other scrub studies, Varghese et al reported a case fatality rate of 9.0% (23). The mortality in Griffith et al was high (24.1%) as it included only critically ill patients (2).

On comparing the myocarditis group with the group without myocarditis, there was no significant difference in the baseline characteristics, symptomatology and laboratory parameters.

On comparing the scoring system, there was a significant difference in patients with cardiovascular failure between the myocarditis group and without myocarditis group ($p<0.006$), and there was no significant difference in the APACHE score between the two groups.

On comparing secondary outcomes, there was significant difference in the need for ICU care ($p<0.051$), ventilation ($p<0.05$), vasoactive agent support ($p<0.00$), duration of ICU ($p<0.047$) and hospital ($p<0.014$) days. There was no significant difference in the crude mortality.

On bivariate logistic regression analysis to predict factors associated with myocarditis, SOFA score and duration of illness were associated with myocarditis. Myocarditis was associated with increased need for ventilation and prolonged ICU and hospital stay. However on multivariate analysis after adjusting for severity of illness and need for ventilation, only duration of illness was associated with myocarditis odds ratio of 0.72 (95% CI: 0.54-0.95, $p<0.020$), suggesting that patients with myocarditis presented earlier. Chacko et al (3) had described H1N1 patients developing myocarditis tended to present later to the hospital. Hence it can be hypothesized that the myocardial involvement in scrub typhus occurs early in the pathophysiology of the disease resulting in early presentation of these patients as compared to other infectious disease like influenza. The other possibility is that better knowledge of physicians and early recognition of complications of scrub typhus which had resulted in early presentation.

8. CONCLUSION

In this cohort of scrub typhus patients from south India the prevalence of myocarditis was 21%. Myocardial injury was seen in 61.7% and myocardial dysfunction was observed in 30.9% participants. A mild grade of diastolic dysfunction was observed in 18% of the study participants. Pericardial involvement was seen in 51% in the form of mild to moderate pericardial effusion. ECG changes were non specific; sinus tachycardia was the predominant ECG finding in this cohort. The development of myocarditis increased the need for ventilation, prolonged the duration of ICU and hospital stay. Myocarditis was not associated with worse mortality in our cohort.

9. SUMMARY OF CONCLUSIONS

1. The prevalence of myocarditis in this cohort of patients was 21%.
2. Myocardial dysfunction was seen in 30.9% of the study participants.
3. Myocardial injury was seen in 61.7% of the study participants (over estimated by the presence of renal failure and critically ill patients)
4. The prevalence of diastolic dysfunction was observed in 18% of the study participants.
5. Pericardial involvement was seen in 51% of the study population in the form of mild to moderate pericardial effusion.
6. ECG changes were non specific; sinus tachycardia was the predominant ECG finding in this cohort.
7. The development of myocarditis increased the need for ventilation, prolonged the duration of ICU and hospital stay.
8. Myocarditis was not associated with worse mortality in our cohort.

10. LIMITATIONS

There were a few difficulties encountered during our study. Firstly though it's a descriptive study our sample size was small. To obtain an adequate transthoracic echo view in certain participants were difficult. It was difficult with a poor echo window to calculate other parameters like cardiac index and systemic vascular resistance index. Some patients were excluded from study due to poor echo window and inability to get adequate echocardiography parameters.

The cardiac biomarker used, troponin T though it was sensitive it lacked specificity resulting probably in overestimation of myocardial injury. A diagnosis of myocarditis is confirmed by histological conformation of myocardial inflammation in the appropriate clinical setting. This requires endomyocardial biopsy or autopsy finding; however these were not possible in our setting. However we defined myocarditis on the basis of myocardial injury with a coexisting global myocardial dysfunction.

The patients with shock were initiated on vasogenic agents and echo was performed on vasogenic agents. Hence the type of shock could have been altered by the use of vasogenic agents.

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12. ANNEXURES

1) PATIENT INFORMATION SHEET

2) PATIENT CONSENT FORMS

3) DATA ABSTRACTION SHEET

4) DATA WORKSHEET

ANNEXURE 1

PATIENT INFORMATION SHEET

TITLE: Assessment of cardiac manifestations in patients with scrub typhus in a tertiary care centre in South India – A prospective cohort

What is this study about?

This study will determine what proportion of patients with scrub typhus will develop cardiac complications. It also determines individuals at risk of developing such complications and contribution of such complications in poor outcome of these individuals. It will investigate how scrub typhus infection can affect the heart hence in better understanding of the disease process, this will help in treating such patients appropriately and will reduce the poor outcomes.

How does this study work?

Either the patient or the family will be requested to read the information sheet and if you decide to be part of the study a doctor will visit you and collect some information. Blood tests, routinely performed on these patients as basic care. Echocardiogram will be done to access their heart function .This is an non invasive method and does not harm the patient.

What are the risks and discomforts during the study?

All the care you receive during the study will be standard in the treatment of patients presently with similar problems. There is no increased harm in the study. The only difference is the echocardiogram a few blood investigations after forty eight hours and at the time of discharge whether or not you show signs or symptoms of cardiac manifestations.

What will I get out of the study?

The aim of the study is to improve the standard of care in such patients with cardiac manifestations and reduce the poor outcomes in these patients. We believe that the information collected will increase the understanding of this disease and thus help minimize the complications related to this disease.

What happens if I refuse?

There will be no difference in treatment if you refuse to participate in the study. There is no obligation to consent to participate in the study. You will receive the same standard of care given to all patients in this hospital. You may choose to withdraw from the study at any time. There are no penalties for withdrawing from the study.

What happens to the results?

The results of this study will be described in a report which may be published as a paper or presented in a conference. At no time will any identifying characteristics of any of the participants be used. Your privacy will be maintained- your records will be accessed only by the investigators of the study and by your treating physicians.

Any questions regarding the study may be addressed to

Karthik G

P G Registrar

Christian Medical College

ANNEXURE 2

Consent Form

TITLE: Assessment of cardiac manifestations in patients with scrub typhus in a tertiary care centre in South India – A prospective cohort

The results obtained from the study will provide information which will help to treat your condition. Also this will help in providing information so that other subjects with similar illness may be prevented or treated more effectively.

You should understand that your records may undergo review and inspection by the donor supporting this activity. The data obtained in the study is stored in a password protected data base and is accessible for evaluation only with consent of the data base manager at the study center. Every effort will be made to protect the confidentiality of the information provided in so far as it is legally possible.

You should understand that your participation in this study is completely voluntary and that you may withdraw at any time without prejudicing your present or future care. You should understand that should your physician find it necessary and/or in your best interest, he/she may withdraw you from the study.

You should understand that if you wish any further information regarding your rights as a subject for the study, you may contact the doctor who is treating you. You have been given opportunity to ask questions and have had them answered to your satisfaction.

CONCLUSION: I have read and / or understand the consent form. I agree to participate in this research study.

_____	_____	_____	_____
Name of the Subject	Signature of Subject	Date	Thumb print
_____	_____	_____	_____
Name of the Investigator	Signature of Investigator	Date	Thumb print

ANNEXURE 3

TITLE: Assessment of cardiac manifestations in patients with scrub typhus in a tertiary care centre in South India – A prospective cohort

Name: Hospital no: Serial no:

Age: Sex: M/F Height: weight: BSA: Scrub positive Y/ N

Admission source: A&E /ward In hospital transfer: Y/ N DOA: DOD:

Date of ICU admission: No:of ICU days: No:of hospi days: Day of illness(onset of fever)

Symptomatology at presentation: **Co-morbities at admission:**

Symptom	**Duration**	**Symptom**	**Duration**		pregnancy	Hypertension	Chronic smoker
Fever		Altered sensorium			Cardiac arrest	Valvular heart disease	Chronic heart failure
Cough		Breathlessness			CAD	HIV infection	immunosuppressant's
Oliguria		Seizures			CLD	Diabetes	Current malignancy
Myalgia		Skin rash			CRF		others

APACHE II: **SOFA:** **ESCHAR: Y / N.**

TEMP:	HR:	pH:	pO2:	pCO2:	Na:	K:	Lact:
MAP:	RR:	HCO3:	Creat:	TC:	Hct:	GCS:	TB:

SOFA:

Points	**1**	**2**	**3**	**4**
Res PF ratio	**<400**	**<300**	**<200**	**<100**
Coagulation, Plt	**<150**	**<100**	**<50**	**<20**
Liver, bilirubin	**1.2-1.9**	**2.0-5.9**	**6.0-11.9**	**>12**
cardiovascular	**MAP<70**	**Dopa≤5, or dobut any dose**	**Dopa>5, or epi, norepi ≤ 0.1**	**Dopa>15, epi, norepi ≥ 0.1**
CNS,GCS	**13-14**	**10-12**	**6-9**	**<6**
Renal ,creat mg/dl	**1.2-1.9**	**2.0-3.4**	**3.5-4.9**	**>5**

variable	**1(<48hrs)**	**2(96-120)**	**3**
APACHE II			
CPK			
CKMB			

TROP T			
Dobutamine Y/N			
Digoxin Y/N			
Vasopressor score			
PEEP			
CVP/RAP			
Mean airway pressure			
ECG changes			
Echo findings:	**HR: BP: Rhy:**	**HR: BP Rhy:**	**HR: BP: Rhy:**

Findings:	**1(<48hrs)**	**2(96-120hrs)**	**3**
***LVEF (M-mode)**			
***LVOT**			
SVI			
CI			
LVSWI			
SVRI			
dP/dT			
***RWMA (Y/N)**			
***E/A**			
***DCT**			
***E/e'**			
LAP			
***RA/RV dilatation**			
***IAS/IVS shifts**			
***Pericardial effusion**			
***valves**			
Misc details.			

Vasopressor free days: duration of vasopressors:

Ventilation :Y/ N if Y NIV /INV Duration of ventilation: NIV: INV: Total: Duration of ICU stay(days): Duration of hospital stay(days): ICU outcome: Dead/ Alive/ discharged at request/ PVS Hospital outcome: Dead/ Alive/ discharged at request/ PVS.

sex	age	EF	CKMB	TROPT	IGM	Eschar	FEVER	COUGH
1	72	40	23.7	352.2	1	1	10	0
2	57	64	3.29	17.25	1	1	7	0
1	52	57	1.55	12.51	1	1	10	4
2	58	84	2.35	16.86	1	1	10	0
2	76	64	5.7	27.66	1	1	10	0
2	72	62	1.57	63.73	1	0	7	0
2	25	46	3.71	115.4	1	1	9	3
1	33	48	2.37	4.03	1	0	10	0
2	83	54	11.83	78.54	1	1	7	0
2	71	51	6.87	10.6	1	1	10	0
2	44	50	2.99	3	1	1	7	0
1	41	78	3.66	5.62	1	1	14	14
1	53	83	14.29	89.78	1	1	4	2
2	50	71	0.756	6.07	1	1	7	0
1	41	57		14.54	1	1	7	7
2	51	39	6.38	146.5	1	0	5	0
2	61	76	1.56	3	1	0	10	0
1	46	44	4.22	10.39	1	1	4	4
2	59	78	12.12	97.63	1	1	5	0
1	63	65	4.57	11.57	1	1	7	0
1	46	42	2.04	118.1	1	1	10	0
2	23	64	1.87	8.97	1	1	7	7
1	60	49	5.62	20.69	1	1	5	3
2	85	51	15.69	88.6	1	1	7	7
1	56	44	1.6	26.93	1	1	8	0
2	50	46	1.89	13.78	1	1	14	0
2	70	67	2.19	28.16	1	1	10	0
2	42	73	1.09	6.32	1	1	7	0
2	65	82	6.6	60.04	1	1	7	0
2	50	57	1.86	16.11	1	0	7	0
1	70	46	6.67	40.39	1	1	5	0
1	55	53	3.24	11.29	1	0	5	2
1	32	43	61.58	1551	1	1	4	0
1	43	51	14.36	14.1	1	1	7	5
1	23	69	0.56	3	1	0	7	7
2	19	65	3.15	105	1	1	5	5
1	52	60	2.19	9.11	1	1	14	7
1	66	62	4.99	28.22	1	1	10	2
1	58	65	14.38	19.31	1	1	10	0
2	45	64	2.05	3	1	1	10	5
1	67	57	4.15	17.51	1	1	10	0
2	75	32	8.35	26.28	1	1	2	0

1	38	43	0.98	4.3	1	0	3	0
2	35	63	2.32	34.31	1	1	7	0
1	45	60	2.09	18.38	1	0	5	1
1	36	66	1.47	7.76	1	0	14	4
2	20	82	2.82	4.77	1	0	3	0
2	50	54	2.25	512.7	1	1	5	0
2	41	63	2.72	3.52	1	0	14	0

DYS	AMS	VOMITING	HEADACH	MYALGIA	SEIZURES	COMORB	PREG	DM
0	1	1	1	0	0	0	0	0
4	0	0	0	0	0	1	0	0
4	0	0	1	0	0	1	0	0
7	1	0	0	0	0	1	0	0
3	0	0	0	0	0	1	0	0
0	0	0	0	5	0	1	0	1
3	0	0	0	0	0	1	1	0
0	1	1	0	1	1	0	0	0
1	1	0	0	0	0	0	0	0
5	0	0	0	0	0	1	0	0
4	0	0	2	0	0	1	0	1
4	0	0	0	0	0	2	0	1
2	0	0	0	0	0	0	0	0
5	0	5	0	1	0	0	0	0
7	0	0	0	1	0	2	0	1
5	0	0	0	0	0	0	0	0
0	3	0	3	0	0	1	0	0
0	0	0	4	1	0	1	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	7	0	1	0	1
3	0	1	0	3	0	0	0	0
2	0	0	0	0	0	0	0	0
0	1	0	5	5	0	0	0	0
1	1	0	0	0	0	0	0	0
5	0	0	0	0	0	1	0	0
2	0	0	14	14	0	1	0	0
4	0	0	10	0	0	0	0	0
0	1	3	0	7	0	1	0	1
2	0	0	0	0	0	0	0	0
0	0	0	0	1	0	2	0	1
4	0	0	0	1	0	2	0	0
2	0	0	0	5	0	1	0	1
3	0	0	0	0	0	0	0	0

3	0	0	0	0	0	0	0	0
0	0	0	7	7	0	0	0	0
5	0	0	0	0	0	1	1	0
0	0	3	0	7	0	0	0	0
2	0	0	0	7	0	2	0	1
1	1	1	0	1	1	0	0	0
5	0	0	0	0	0	0	0	0
1	0	0	0	0	1	0	0	0
3	0	0	0	0	0	1	0	0
0	0	0	1	0	0	1	0	0
2	0	0	0	5	0	0	0	0
1	0	0	0	0	0	1	0	1
4	0	1	0	4	0	0	0	0
1	0	0	0	0	0	1	1	0
1	2	0	0	0	0	2	0	1
14	0	1	1	1	0	1	0	0
HTN	CAD	SMOK	ALCH	HIV	VHD	CRF	CLD	DL
0	0	0	0	0	0	0	0	0
0	0	0	0	1	0	0	0	0
1	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	1	0	0	0	0		0
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0	0	1	0	0	0	0	0	0
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0	0	0	1	0	0	0	0	0
1	0	0	0	0	0	0	0	0

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0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
0	0	1	1	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
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1	1	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	1
0	0	0	1	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
Resp_dis	Res_fail	Haem_dis	Haem_fail	Liv_dis	Liv_fail	CVS_dis	CVS_fail	CNS_dis
1	0	1	0	1	0	0	1	0
0	1	0	1	1	0	0	0	0
1	0	1	0	0	0	0	0	0
0	1	1	0	1	0	0	1	0
1	0	1	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	1	0	1	0	0	0	1	0
1	0	1	0	0	1	0	0	0
0	1	1	0	1	0	0	1	1
1	0	0	1	0	0	0	0	0
1	0	1	0	0	0	0	1	0
1	0	0	1	1	0	0	0	1
1	0	0	1	1	0	0	1	0
1	0	0	1	0	0	0	0	0
2	0	0	0	0	0	1	0	0
0	1	1	0	0	0	0	1	0
1	0	1	0	1	0	0	0	1
0	0	0	1	1	0	0	0	0
0	1	0	1	1	0	0	1	0

1	0	0	1	0	0	0	0	0
0	1	0	1	0	1	0	1	1
1	0	1	0	1	0	0	1	0
0	1	1	0	0	0	0	1	0
1	0	1	0	1	0	0	1	1
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0	1	1	0	1	0	0	1	0
0	1	0	1	0	0	0	2	0
1	0	0	1	1	0	0	0	0
0	1	0	1	0	0	0	1	0
1	0	0	1	0	0	1	0	0
1	0	0	1	1	0	0	0	0
0	0	1	0	1	0	0	0	0
0	1	0	1	1	0	0	1	0
1	0	0	1	1	0	0	1	1
1	0	1	0	0	0	0	0	0
0	0	0	1	0	0	0	1	0
0	0	0	1	1	0	0	0	0
0	1	0	1	1	0	0	1	0
0	1	0	1	1	0	0	1	0
0	1	0	1	1	0	0	1	0
1	0	0	1	1	0	0	1	0
1	0	1	0	0	0	0	1	1
0	0	0	1	0	0	0	0	0
1	0	1	0	1	0	0	0	0
0	0	1	0	0	1	0	0	0
1	0	1	0	1	0	1	0	0
1	0	1	0	0	0	0	1	0
1	0	0	1	0	0	0	0	1
0	0	0	1	0	1	0	0	0
CNS_fail	Ren_dis	Ren_fail	SOFA	APACHE	APACHE_pred	Dialysis	CREAT	DOBUT
1	0	1	15	35	83.1	1	4.5	0
0	0	0	8	18	29.1	0	1	0
0	1	0	5	12	14.6	0	1.32	0
0	0	1	13	22	42.4	0	3.7	0
0	0	0	4	12	14.6	0	1.02	0
0	1	0	1	15	21	0	1.75	0
0	0	0	10	13	16.5	0	0.89	0
1	0	0	8	12	14.6	0	0.8	0
0	1	0	12	22	42.4	0	1.48	0
0	1	0	7	12	14.6	0	1.46	0
0	1	0	8	19	32.2	0	2.45	0
0	1	0	8	16	23.5	0	1.2	0

0	0	1	14	26	56.9	0	3.6	1
0	0	0	5	6	6.7	0	0.84	0
0	0	0	3	10	11.3	0	1.08	0
0	1	0	12	23	46	0	2.47	1
0	0	0	8	17	26.2	0	0.92	0
0	1	0	7	7	7.6	0	1.2	0
0	0	0	12	11	12.9	0	1.08	0
0	0	0	6	13	16.5	0	1.16	0
0	1	0	18	30	70.3	0	2.44	1
0	0	0	9	5	5.8	0	0.68	0
0	0	0	10	15	21	0	1.06	0
0	1	0	11	24	49.7	0	1.45	0
0	1	0	10	19	32.2	0	1.8	0
0	0	0	10	12	14.6	0	0.92	0
0	0	0	10	14	18.6	0	1.19	0
1	1	0	10	17	26.2	0	1.56	0
0	0	0	11	16	23.5	0	1.04	1
0	1	0	7	18	29.1	0	1.58	0
0	0	0	6	11	12.9	0	1.12	0
0	1	0	4	19	32.2	0	1.69	0
0	1	0	13	4	5.1	0	1.21	0
0	1	0	14	20	35.5	0	1.35	0
0	1	0	5	8	8.7	0	1.29	0
0	0	0	6	10	11.3	0	0.8	0
0	1	0	5	16	23.5	0	1.2	0
0	1	0	14	20	35.5	0	3.04	0
1	1	0	16	31	73.3	0	2.72	0
0	1	0	14	15	21	0	1.43	0
0	1	0	12	15	21	0	3.04	0
0	0	0	8	21	38.9	0	0.95	
0	1	0	4	11	12.9	0	1.54	0
0	0	0	4	4	5.1	0	0.99	0
0	1	0	7	14	18.6	0	3.19	0
0	0	0	7	9	9.9	0	1.18	0
0	0	0	7	15	21	0	0.78	0
0	0	0	6	7	7.6	0	0.89	0
0	0	0	6	11	12.9	0	0.45	0
DIGOXIN	dopa	adr	norad	vaso score	VENT	NIV	INV	LVEF
0	0	0	1		1	1	0	40
0	0	0	0	0	1	1	0	64
0	0	0	0	0	0	0	0	57
0	1	0	1		1	0	1	84

0	0	0	0	0	0	0	0	64
0	0	0	0	0	0	0	0	62
0	1	0	1		1	0	1	46
0	0	0	0	0	1	0	1	48
1	1	1	1		1	1	1	54
0	0	0	0	0	0	0	0	51
0	1	0	1		1	0	1	50
0	0	0	0	0	0	0	0	50
0	1	1	1		1	0	1	83
0	0	0	0	0	0	0	0	71
0	0	0	0	0	0	0	0	57
1	0	1	1		1	0	1	39
0	0	0	0	0	0	0	0	76
0	0	0	0	0	0	0	0	44
0	1	0	1		1	0	1	78
0	0	0	0	0	0	0	0	65
1	0	0	1		1	0	1	42
0	0	1	1		1	1	0	64
0	0	1	1		1	0	1	49
1	1	1	1		1	1	1	51
0	0	0	1		1	1	1	44
0	1	1	1		1	0	1	46
0		0	1		1	1	1	67
0	0	0	0		1	0	1	51
1	1	1	1		1	0	1	82
0	0	0	0		0	0	0	57
0	0	0	0		0	0	0	46
0	0	0	0		0	0	0	53
1	1	0	1		1	1	0	43
0	1	1	0		1	0	1	33
0	0	0	0		0	0	0	69
0	1	0	1		1	1	0	65
0	0	0	0		0	0	0	60
0	0	0	1		1	0	1	62
0	1	0	1		1	0	1	65
0	0	1	1		1	0	1	64
0	0	0	1		1	0	1	57
	0	1	1		1	0	1	32
0	0	0	0		0	0	0	43
0	0	0	0	0	0	0	0	63
0	0	0	0	0	0	0	0	60
0	0	0	0	0	0	0	0	66
0	1	1	1		1	0	1	82

0	0	0	0	0	0	0	0	48
0	0	0	0	0	0	0	0	63
LVOT	VENT	NIV	INV	CVP	VTI	CO	SV	CI
2.12	1	1	0	15	17.3	4.4	61.07	2.4
1.8	1	1	0	5	20.4	5.19	51.91	3.31
1.91	0	0	0	20	22.9	5.9	65.61	2.99
2.36	1	0	1	5				
1.84	0	0	0	10	31.2	5.06	85.69	3.89
1.32	0	0	0	10	26.4	2.96	36.13	1.96
1.98	1	0	1	5	16.1	6.99	49.57	4.48
2.17	1	0	1	15	21.8	5.16	80.62	3
1.59	1	1	1	20	16.7	3.85	33.16	2.35
1.97	0	0	0	15	21.1	5.92	64.31	3.68
1.93	1	0	1	15	18	4.74	52.66	2.96
1.95	0	0	0	15	21.1	4.79	63.01	2.58
1.38	1	0	1	15	17.00	3.51	25.43	1.87
1.75	0	0	0	15	22.3	5.15	53.64	2.68
1.84	0	0	0	15	16.8	3.71	44.67	2.2
1.72	1	0	1	20	14.4	2.48	33.46	1.31
1.65	0	0	0	5	23.4	4.5	50.03	2.6
1.68	0	0	0	10	21	3.72	46.55	2.16
1.87	1	0	1	10	19.5	5.62	53.56	3.39
2	0	0	0	5	13.2	3.7	41	2.09
1.65	1	0	1	15	23.8	5.9	51	2.12
1.48	1	1	0	20	22.3	4.6	38.36	3.19
1.68	1	0	1	15	12.1	2.8	27	1.77
1.59	1	1	1	5	27	5	54	3.05
2.35	1	1	1	10	16.2	7.8	70	4.41
1.53	1	0	1	20	18.9	3.4	35	2.13
1.94	1	1	1	10	17.6	5.6	52	3.54
1.97	1	0	1	10	16.4	4.6	50	2.86
1.41	1	0	1	10	7.39	1.4	12	1.08
2.06	0	0	0	15	17.3	5.1	58	3.15
2.34	0	0	0	15	17.4	6.8	75	4.28
1.76	0	0	0	15	15.1	3.9	37	2.23
1.55	1	1	0	10	15.2	2.9	29	1.65
1.61	1	0	1	10	15.1	3.6	31	2.09
1.96	0	0	0					
2.17	1	1	0					
1.72	0	0	0	5	19.3	4.1	45	2.29
1.74	1	0	1					
1.73	1	0	1	15	14.8	4.1	35	2.52
1.42	1	0	1	5	21.9	3.6	35	2.52

1.93	1	0	1	5				
1.75	1	0	1	5	16.6	5.8	40	3.79
1.81	0	0	0	5	17.7	3.3	46	1.74
1.62	0	0	0	15	23.6	3.9	49	2.15
1.9	0	0	0	5	20.6	4.1	58	3.15
2.03	0	0	0	5	16.6	5.6	54	3.37
1.43	1	0	1					
1.72	0	0	0	15	14.4	3.45	33.46	2.17
2.05	0	0	0	5	19.3	6.69	63.7	4.58
SVI	LVSWI	MAP	SVRI	RWMA	E/A	E/e	EFFUS	ICU
0.03	0.0205	72	1035.07	0	1.38	12.9	1	1
0.03	0.03	77	1738.01	0	1.17	6.18	1	1
0.03	0.04	87	1790.4	0	1.79	7.82	1	0
		83		0	0.78	5.79	0	1
0.07	0.09	87	1581.57	0	0.89	10.9	1	0
0.02	0.03	97	3546.58	0	1.07	16.2	1	0
0.03	0.03	74	1230.6	1	0.89	7.9	1	1
0.05	0.07	93	2077.4		1.62	5.99	1	1
0.02	0.03	90	2380	1	1.58	16.1	1	1
0.04	0.05	86	1541.55	0	0.84	13.6	1	1
0.03	0.04	84	1862.53	1	1.32	13.4	0	1
0.03	0.03	76	1889.11	1	1.51	8.85	0	0
0.01	0.01	85	2990.91	0	0.66	5.43	1	1
0.03	0.04	90	2236.01	0	1.25	10.5	1	0
0.03	0.03	80	2360.68	0	0.93	11	1	0
0.02	0.02	79	3598.55	1	2.09	14.4	1	1
0.03	0.04	83	2397		0.69	7.73	0	0
0.03	0.04	93	3255.19	0	1.02	8.86	1	0
0.03	0.03	63	1249.17	0	1.33	1.33	1	1
0.02	0.02	73	2599.62	0	0.94	9.94	0	0
0.02	0.03	87	2713.58	1	0.98	6.13	1	1
0.03	0.03	73	1327.49	0	1.24	9.47	0	1
0.02	0.03	87	3250.17	0	0.72	7.27	1	1
0.03	0.03	76	1859.97	0	1.58	16.1	0	1
0.04	0.06	97	1576.26	0	1.16	7.43	1	1
0.02	0.02	77	2138.17	0	0.98	9.59	1	1
0.03	0.04	82	1625.08	1	0.65	4.71	1	1
0.03	0.04	86	2123.22		0.84	13.6	1	1
0.01	0.01	75	4808.8		2.3	18.9	1	1
0.04	0.05	93	1978.48		0.91	9.44	0	0
0.05	0.07	93	1456.12		0.78	18.7	1	0
0.02	0.03	103	3153		0.77	8.03	1	0
0.02	0.03	90	3873.94		0.92	5.48	0	1

0.02	0.03	91	3096.6		0.69	8.04	0	1
		83			1.39	6.47	1	0
		75			1.41	6.79	0	1
0.03	0.04	87	2861.05		1.3	11.8	1	0
		62			0.71	12.1	0	1
0.02	0.02	79	2029.21		1.1	6.76	0	1
0.02	0.02	69	2029.21		0.86	11.9	1	1
					1.08	13.8	0	1
0.03	0.03	79	1560.05		0.71	7.11	0	1
0.02	0.02	73	3104.69		1.76	5.69	0	0
0.03	0.03	80	2415.58		2.13	10.7	0	0
0.05	0.06	87	2079.94		1.19	10.1	1	0
0.03	0.03	70	1541.1		1.28	12.5	0	0
		69			1.8	8.89	0	1
0.02	0.03	97	1899.07		1.29	11.2	0	0
0.04	0.05	90	1482.86	1	1.08	8.71	1	0

ICU_LOS	Hosp_LOS	ICU_OUT	HOSP_OUT	DYS	MCI	myocard
2	9	0	0	1	1	1
3	8	0	0	0	1	0
0	9	0	0	0	0	0
9	14	0	0	0	1	0
0	5	0	0	0	1	0
0	9	0	0	0	1	0
5	9	0	0	1	1	1
5	9	0	0	1	0	0
4	9	0	0	0	1	0
2	7	0	0	0	0	0
8	11	0	0	1	0	0
0	5	0	0	0	0	0
13	13	1	1	0	1	0
0	5	0	0	0	0	0
0	3	0	0	0	1	0
6	11	0	0	1	1	1
0	6	0	0	0	0	0
0	6	0	0	1	0	0
7	11	0	0	0	1	0
0	4	0	0	0	0	0
8	13	0	0	1	1	1
4	8	0	0	0	0	0
8	18	0	0	1	1	1
4	9	0	0	0	1	0
8	12	0	0	1	1	1
19	24	0	0	1	0	0

13	16	1	1	0	1	0
5	8	0	0	0	0	0
3	3	1	1	0	1	0
0	8	0	0	0	1	0
0	9	0	0	1	1	1
0	6	0	0	0	0	0
6	8	0	0	1	1	1
4	5	1	1	0	0	0
0	5	0	0	0	0	0
3	6	0	0	0	1	0
0	8	0	0	0	0	0
11	19	0	0	0	1	0
6	9	0	0	0	1	0
9	10	0	0	0	0	0
11	20	0	0	0	1	0
2	2	1	1	1	1	1
0	6	0	0	1	0	0
0	3	0	0	0	1	0
0	7	0	0	0	1	0
0	4	0	0	0	0	0
12	15	0	0	0	0	0
0	5	0	0	0	1	0
0	9	0	0	0	0	0